10

T Lymphocytes, Natural Killer Cells, Cytokines, and Immune Regulation

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Systemic lupus erythematosus (SLE) is a systemic disease that is characterized by generalized autoimmunity. Unlike organ-specific autoimmune diseases such as insulin-dependent diabetes mellitus or myasthenia gravis, SLE is characterized by autoantibodies against nuclear, cytoplasmic, or cell surface molecules that transcend organ-specific boundaries. It is the inflammatory responses triggered by local formation and/or deposition of antigen–antibody immune complexes that are responsible for the clinical manifestations of vasculitis and multiorgan system disease (1).

For over 20 years, SLE had been considered to be primarily a B-cell disease, as reflected by hyperactivity of the humoral component of the immune response (2–5) and concomitant T-cell hypoactivity (6–8). However, we now appreciate that like most (if not all) autoimmune diseases, SLE is T-cell dependent. In murine models of SLE, depletion of CD4+ T cells blocks disease onset (9), and athymic mice do not develop SLE (10, 11). In humans, the effects of human immunodeficiency virus (HIV) infection on CD4+ lymphocytes may ameliorate SLE activity and spur remission (12).

During the past few years, concepts concerning antigen recognition by T cells have been revised. Self-recognition had been considered to be pathologic, and self-reactive T cells were believed to be eliminated completely during ontogeny. In contrast, it now is appreciated that the mechanisms underlying T-cell recognition of and response to both foreign and self-antigens are similar. Reactivity to self histocompatibility molecules by T cells is not only physiologic, it is indispensable to the generation of normal immune responses. Moreover, clonal deletion of T cells that are capable of reacting against certain self-peptides is incomplete, demonstrating that autoreactive T cells normally persist (13).

With the realization that every individual harbors T cells that could potentially induce autoimmune disease, it becomes necessary to understand the mechanisms that initiate and sustain nonresponsiveness or tolerance. Just as autoreactive T cells are not completely eliminated during ontogeny, B cells that have the potential to make autoantibodies also are not completely deleted (14). IgM autoantibodies with anti-DNA or anti-IgG (i.e., rheumatoid factor) specificities may arise through nonspecific (i.e., T cell–independent) stimulation of B cells (15, 16). Because they are of the IgM class, these autoantibodies generally are not pathogenic. However, following the breakdown of tolerance in SLE, normally quiescent T cells become activated (17–19). These T cells provide the necessary help for IgM-producing B cells to undergo class switching and secrete pathogenic IgG anti-DNA (20, 21). As discussed later, many discrete and seemingly disparate T-cell abnormalities may lead to this same, common end result. Moreover, ineffective attempts by the immune system to downregulate the ongoing autoimmunity may lead to a variety of secondary T-cell abnormalities.

Before reviewing immune abnormalities in SLE in this chapter, present concepts of T-cell development and function in normals are summarized to provide the reader with essential background information. Two caveats are offered at the outset. First, present concepts of immune dysregulation in SLE largely have been derived from studies involving murine models of SLE. The great advantages of

murine models are that in vivo studies can be undertaken and the lymphoid organs, where autoimmunity is generated and sustained, can be studied directly. In contrast, most of the information concerning human SLE has been derived from the study of blood lymphocytes, and one can never be absolutely certain that the ex vivo properties of blood lymphocytes precisely reflect those events occurring in lymphoid organs in vivo. Second, while human SLE typically is a disease of exacerbations and remissions even in the absence of immunosuppression medications, animal models generally have a progressive course. Dynamic regulatory mechanisms therefore are especially important in human SLE. Confusing the picture further is the heterogeneity of SLE syndromes and the differences in patient populations studied by individual investigators. Nonetheless, in general, studies of blood lymphocytes in human SLE have complemented those in murine lupus and shed considerable light on the immune dysfunctions underlying SLE.

General Properties of T Cells

T cells are thymus-derived lymphocytes that develop either regulatory or effector functions. Unlike B cells, T cells are unable to bind antigen directly; rather, they recognize antigen in conjunction with self class I or class II molecules of the major histocompatibility complex (MHC). The T-cell antigen receptor (TCR) is expressed on the surface of T cells and consists of a two-chain heterodimer antigen-binding unit (either α and β chains or γ and δ chains) that is noncovalently complexed to the signal-transducing CD3 structure.

The CD4 molecule recognizes a monomorphic region of class II molecules. Therefore, CD4+ lymphocytes, as a rule, recognize antigen in combination with self class II (HLA-DR, DP, DQ) MHC gene products. Typically, phagocytic cells ingest extracellular microbes such as bacteria, and after antigen processing, small peptides are complexed to MHC class II and expressed on the cell surface for presentation to CD4+ cells. Monocytes, dendritic cells, and other HLA-DR+ antigen-presenting cells interact with CD4+ cells in this manner.

The CD8 molecule recognizes a monomorphic region of class I MHC molecules. Therefore, CD8+ T cells, as a rule, recognize peptide fragments that are bound to class I (HLA-A, B, C) MHC molecules. In this way, CD8+ cells can eliminate cells that are infected by intracellular organisms. Viral proteins that are synthesized by infected cells are degraded by proteases, and these peptides are complexed to MHC class I molecules and translocated to the cell surface for recognition by CD8+ cells.

Although CD4+ cells usually provide B-cell help and CD8+ cells downregulate antibody production or become killer cells (22), each of these populations can develop the opposite function (23, 24).

The great majority of CD4+ and CD8+ T cells express TCR $\alpha\beta$ chains, whereas the few T cells that lack both CD4 and CD8 molecules (CD3+ CD2+ CD4- CD8-) cells usually express $\gamma\delta$ chains. However, the TCR $\gamma\delta$ cells also may be CD4+ or CD8+. Although only a small number of these cells circulate in the blood, they are enriched in the skin, lung, gastrointestinal tract, and the female reproductive tract (Table 10.1).

Table 10.1. Human T Lymphocyte Populations.

TCR Chains	Population	Comment
$\alpha\beta$	CD4+ cells	Recognize peptide antigens complexed to self MHC class II structures (HLA-DR, DP, DQ)
	CD4+ cells	Recognize peptide antigens complexed to self MHC class I structures (HLA--A, -B, -C)
	CD4− CD8−	Minor population
$\gamma\lambda$	CD4− CD8−, CD8+	Minor population in blood; large percentage of intraepithelial lymphocytes found in the skin, small intestine, female reproductive tract, and the lungs; recognize CD1, lipid antigens.

Mechanisms Involved in Tolerance Induction and Maintenance

Clonal Deletion

During ontogeny, pluripotent stem cells migrate to the thymus and become thymocytes, which potentially are capable of differentiating into mature T cells. However, only a small percentage of thymocytes actually survive intrathymic development and fully mature into immunocompetent T cells. This is the result of two processes, termed *positive* and *negative selection*. Positive selection refers to those events through which only those T cells that recognize self-MHC are allowed to survive (25). These T cells recognizing self-MHC class II or class I molecules become CD4+ or CD8+ cells, respectively. Through a sequence of events called negative selection, these T cells migrate to the thymic medulla, where those T cells that bind strongly to self-peptide–MHC complexes presented by stromal cells are eliminated (25). In this manner, only T cells that are capable of recognizing self-MHC molecules reach the periphery, but those T cells with exceptionally avid autoreactivity (i.e., potential autoaggressive T cells) are physically deleted from the T-cell repertoire (Table 10.2).

Table 10.2. Mechanisms Involved in T lerance Induction and Maintenanc

Mechanism	Site	Comment
Clonal deletion	Thymus and periphery	Not all potentially autoaggressive T cells are deleted from the repertoire. In the periphery, these cells are deleted by activation-induced cell death.
Clonal anergy	Thymus and periphery	T cells that recognize self peptides Signal 1 without the required co-stimulatory signal (signal 2) become non responsive. Clonal anergy is reversible.
Regulatory cells	Periphery	Although there is unequivocal evidence of antigen-specific and non-specific suppression, the cellular mechanisms involved have been poorly understood.
Clonal ignorance	Periphery	Self-reactive cells exist in the periphery but remain immunologically dormant because of a lack of T cell activation. Infectious agents bearing antigens similar to self can activate these T cells.

Clonal Anergy and Activation-Induced Cell Death

Because thymic stromal cells lack many important tissue-specific autoantigens, clonal deletion of potential autoaggressive T cells in the thymus is incomplete. Studies with transgenic mice have revealed that some potentially autoaggressive T cells do physically exist, but they are rendered anergic (i.e., immunologically nonresponsive) (13, 26) in the periphery. T cells require at least two signals to proliferate or develop effector function: specific antigen (signal 1), and a critical costimulatory signal (signal 2). The latter signal is generated following CD28 binding on the T-cell surface to B7.1 or B7.2 (CD80 or CD86) expressed by the accessory cell (27, 28). If T cells bind antigen in the absence of proper costimulatory signals, they have two possible outcomes. First, they may undergo a series of events that prevents them from becoming activated by antigen at a later time (29); this is called *clonal anergy*. Alternatively, they may proliferate briefly but then undergo apoptosis; this is called *activation-induced cell death* (30). Because anergic cells physically persist, this nonresponsiveness can be reversed by certain cytokines, such as IL-2 (31). Thus, bystander autoreactive, anergic-state T cells may be converted into fully competent, autoaggressive T cells that are capable of promoting an autoimmune response if, by chance, anergic cells find themselves in close proximity to other cells producing IL-2 in response to some unrelated foreign antigen.

Regulatory Cells

A third mechanism through which potentially autoaggressive T cells could be kept in check is through one or more lymphocyte populations with downregulatory activity that can inhibit antibody synthesis by B cells or suppress responses by effector T cells. CD8+ T cells have been considered to be the principal source of suppressor cells, but CD4+ can develop this function as well (32). The existence of a separate lineage of antigen-specific T-suppressor cells is controversial, because few T-suppressor clones demonstrate rearrangement of the genes that encode the T-cell antigen receptor.

Regardless of whether true antigen-specific suppressor T cells exist or functional suppression is predicated through more conventional mechanisms such as auto-anti-idiotypic responses, there is persuasive evidence that one or more T-cell subsets in the adult host have a surveillance function and suppress autoimmunity. In murine models, passive transfer of T cells from nonautoimmune strains to genetically identical, athymic adult animals induces autoimmunity (33), because the recipients lack the necessary suppressor cells to downregulate autoaggressive donor T cells. Second, in the induction of arthritis by passive transfer of autoimmune T-cell clones, the recipients first must be irradiated or pretreated with cyclophosphamide to eliminate T cells that block autoimmunity (34).

Some T cells have the capacity to recognize antigen receptors on lymphocytes. The peptide fragments of the antigen receptor that are recognized are called *idiotypes*, and idiotype-specific helper T cells have been identified. Anti-idiotypic self-recognition is important in immune regulation, as discussed elsewhere in this volume.

Clonal Ignorance

T cells with low-affinity receptors for organ-specific self-antigens (i.e., thyroid, pancreatic islet cell) may escape both clonal deletion and clonal anergy. Transgenic mouse models of autoimmune disease have revealed the existence of competent T cells that are specific for self-peptides and that under normal physiologic conditions fail to react with these self-peptides. Following a microbial infection, however, these cells become activated and can initiate autoimmunity (35).

Postthymic T-Cell Maturation

T-cell maturation is not complete when a T cell leaves the thymus; exposure to antigen in the periphery is required to complete the maturation process. Neonatal CD4+ peripheral T cells have low avidity for antigen, and on stimulation, they produce IL-2 but few other cytokines (36). These T cells are considered to be "virgin" or "naive." After antigenic stimulation, avidity for antigen increases, presumably caused by upregulation of adhesion molecules with costimulatory activity. These T cells are termed *mem-*

ory cells, because they can be stimulated by antigen under much less stringent conditions (37–40). Such CD4+ cells respond well to soluble antigens and support B-cell differentiation. Corresponding memory CD8+ cells, which are the precursors of antigen-specific killer cells, also are generated (41, 42). Naive and memory T cells can be identified phenotypically by reciprocal expression of CD45 isoforms on their cell surfaces. (CD45 is a membrane tyrosine phosphatase that has a vital role in signal transduction). Naive T cells display the high-molecular-weight CD45RA isoform, and memory T cells express the low-molecular-weight CD45RO isoform (37–40).

This distinction between naive and memory T cells is especially important in the development of autoimmunity, because T cells that are capable of recognizing self-peptides are presumably in the immature, naive state. As discussed, through clonal anergy or T-cell suppression, these cells will not have been permitted to proliferate and mature into memory cells. Once autoreactive T cells are able to reach the memory stage, autoimmunity would be easy to sustain, because of the relative ease of their activation by antigen.

Physiologic T-Cell Regulation of Antibody Production

Generation of antibodies in response to most antigens is T cell–dependent. The T-cell contribution to antibody synthesis can be subdivided into antigen presentation and activation of CD4+ T cells; cell-to-cell interactions between T, B, and other cells; cytokine production by these activated cells; and the resulting B-cell differentiation. (Antigen presentation to CD4+ cells was discussed earlier.)

Early Activation Events

Although it may be naive to believe that only a few biochemicals generated intracellularly can completely control T-cell fate, it is well established that certain such biochemicals (i.e., intracellular second messengers) are indeed crucial to ultimate T-cell responses. Binding of ligand to T-cell surface CD3/TCR triggers a sequence of events leading to phospholipase C activation with hydrolysis of phosphatidylinositol-1,4-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol 1,4,5-trisphosphate ($1,4,5\text{-}IP_3$) (43). DAG is the physiologic activator of protein kinase C (PKC) (44); $1,4,5\text{-}IP_3$ promotes calcium mobilization from internal stores and, in T cells, may promote calcium influx across the plasma membrane as well (45). In addition to the role of PIP_2 hydrolysis in generating intracellular DAG, a major portion of intracellular DAG generation (leading to PKC activation) also may arise via hydrolysis of phosphatidylcholine (46, 47).

Changes in the intracellular free-calcium concentration play a key role in T-cell activation. Elevations in intracellular free-calcium levels through mobilization of intracellular stores may not generate the same functional consequences to the cell as elevations of intracellular free calcium through influx of extracellular calcium (48). Influx of exogenous calcium is critical, because depletion of extracellular calcium with chelating agents or pharmacologic blockade of calcium channels profoundly inhibits lymphocyte activation (49, 50), and calcium chelators may affect gene expression and production of vital lymphokines such as IL-2 (51).

Other early activation-associated biochemical events include the activation of several protein tyrosine kinases such as $p56^{lck}$ and $p59^{fyn}$, activation of PKC, and generation of cyclic AMP (cAMP). Activation of PKC is absolutely essential for IL-2 production (52), and inhibition of PKC activity correlates well with inhibition of T-cell proliferation (53). On the other hand, increased intracellular levels of cAMP correlate with inhibition of IL-2 production by and proliferation of T cells, presumably by activating protein kinase A (PKA) (54).

Co-stimulatory Effects From Cell to Cell Interactions

As indicated earlier, T cells do not recognize isolated antigen. Rather, they recognize antigen only in the context of self-MHC molecules that are expressed on the surface of the antigen-presenting cell. In addition to the binding of antigen to CD3/TCR, T cells require one or more costimulatory signals for proliferation and differentiation that are supplied by antigen-presenting and other interacting cells (29). As stated, the ligation of T-cell CD28 with CD80/CD86 (formerly B7.1 and B7.2) molecules on antigen-presenting cells prevents T cells from undergoing apoptosis, or programmed cell death. Importantly, CD80/CD86 molecules also are expressed on activated B cells, especially those committed to produce IgG (55, 56). Thus, activated B cells may further enhance T-cell activation and IL-2, leading to even further enhanced IgG production by B cells (57).

Other T-cell surface antigens that are upregulated during an immune response that play vital roles in T-cell helper function and T-cell cytolytic function, respectively, are CD40 ligand and Fas ligand. CD40 ligand, by interacting with CD40 on the surface of B cells, can deliver a differentiation signal as well as either rescuing B cells from or priming B cells for apoptosis (58–64). CD40 ligand is transiently expressed by CD4+ T cells soon after activation and is quickly downregulated, especially in the presence of B cells (65, 66). This tight regulation of CD40 ligand expression presumably protects the host against the induction of indiscriminate polyclonal B-cell differentiation by activated T-helper cells. It remains to be established whether dysregulated CD40 ligand expression by T cells occurs in SLE and what role, if any, this plays in the characteristic hypergammaglobulinemia and/or autoantibody production.

Fas ligand expression by T cells plays an important role in triggering Fas-based apoptosis of Fas+ target cells. Fas

based cell death represents an essential regulatory pathway for activated T cells and, under certain circumstances, for activated B cells as well (67–76). Unfortunately, Fas ligand expression has been more difficult to detect than CD40 ligand expression, because for human T cells, there have been no reagents sensitive enough to detect measurable amounts of Fas ligand on the surfaces of intact T cells. As a consequence, Fas ligand usually has been measured at the mRNA level. Very recently, the ability to detect surface Fas ligand expression by flow cytometry has been demonstrated using hydroxaminic acid–based metalloproteinase inhibitors (77), so surface Fas ligand expression may become quantifiable. Regulation and kinetics of Fas ligand expression are topics of intense, active research, and we anticipate that important insights will be garnered during the next few years regarding the role of Fas ligand dysregulation in SLE.

Other examples of interactions that promote lymphocyte growth and differentiation include lymphocyte function antigen 3 (LFA-3 or CD58), which binds to the CD2 molecule on T cells, and intracellular adhesion molecule 1 (ICAM-1 or CD54), which binds to another T-cell surface structure called LFA-1 (or CD11a). In some cases, adhesion molecules may have signal-transducing properties (78).

The Role f Cytokines

Cytokines are hormone-like factors that are produced and secreted by various cell types during the course of an immune response. They generally act at short distances to affect the function of the cells that produce them (i.e., autocrine effects) and the function of other cells in the immediate vicinity (i.e., paracrine effects). Some, such as IL-6, also can act at long distances. The effects of cytokines on T cells are complex. Certain cytokines form cascades or interactive networks that regulate each other as well as the growth, differentiation, and effector function of responding cells.

Table 10.3 presents a convenient classification of selected cytokines based on the capacity to support either cellular or humoral immunity. Those that preferentially support cell-mediated immunity are indicated as type 1 cytokines (IL-2, interferon (IFN)-γ, IL-12) and those that

Table 10.3. Major Cytokines involved in Humoral and Cellular Immunity

Type I Cytokines	Predominant effect is to support cell-mediated immunity*	
Interleukin 2	Produced by T cells	Essential T cell growth factor; involved in the induction of T killer cells and regulatory cells
Interferon gamma	Produced by T cells and NK cells	Involved in macrophage activation and induction of killer cell activity Also enables B cells to produce complement fixing IgG antibodies Can also co-stimulate B cell differentiation
Interleukin 12	Principal source—macrophages Also produced by B cells	Crucial role in host defense against intracellular microbial agents. Co-stimulates T cell activation and differentiation Can also co-stimulate B cell differentiation
Type II cytokines	Predominant effect is to support antibody production*	
Interleukin 4	Produced by T cells and basophils	Elevated levels in parasitic and allergic diseases associated with high levels of IgE Anti-inflammatory effect: decreases the production of Type I cytokines
Interleukin 6	Produced by Macrophages, T cells and B cells	Involved in B cell growth and differentiation Also can enhance T killer cell activity
Interleukin 10	Major source—macrophages Also produced by T cells and B cells	Major B cell growth factor Anti-inflammatory effect: decreases the production of Type 1 cytokine Blocks antigen-presentation to T cells
Other cytokines		
Interleukin 1	Major source—macrophages	Part of a cytokine cascade which includes IL-6 and TNFα Stimulates macrophages to produce PGE2
Tumor necrosis factor-alpha	Produced by macrophages NK cells and T cells	B cell differentiation factor Major pro-inflammatory effects Involved in regulatory cell differentiation
Transforming growth factor-beta	Major source—macrophages and NK cells	Produced as an inert latent complex (must be converted to active form Major immunosuppressive effects Critical co-factor in the generation of regulatory cells

*Notwithstanding the predominant effects of Type I and Type II cytokines, many of these cytokines have potent effects on both normal and cell-mediated immunity as indicated.

predominantly provide help for antibody production are indicated as type 2 cytokines (IL-4, IL-5, IL-6, IL-10) (79, 80). Either lymphocytes or nonlymphoid cells may serve as the principal source of these cytokines. Regarding type 1 cytokines, IL-2 is produced by T cells, IFN-γ is produced by both T and natural killer (NK) cells. IL-12 is produced by monocytes (81). With respect to type 2 cytokines, IL-4 is made by T cells and basophils and IL-10 by T, B, and monocytes (82), with the latter being the primary source. Tumor necrosis factor–α (TNF-α) is not classified as either a type 1 or type 2 cytokine, but it does have a major role in the pathogenesis and perpetuation of SLE (discussed later). This cytokine is produced predominantly by mononuclear phagocytes (83) as well as by NK and T cells (84). Transforming growth factor–β (TGF-β) is produced predominantly by macrophages (85) and NK cells (85a), but can also be synthesized by T cells (86).

With persistent antigen stimulation and conditioning by type 1 and type 2 cytokines, T cells can be polarized into subsets that develop distinct effector functions (80). IL-12 can condition CD4+ T cells to become cytotoxic effector cells, whereas type 2 cytokines can condition CD4+ T cells to provide B cell help. IL-4 upregulates IgG4 and IgE production, but it inhibits production of other immunoglobulin isotypes (87), perhaps through its inhibitory effects on monocytes (88, 89). IL-6 serves as an important growth factor for activated B cells in the late phase of B-cell differentiation (90). This dichotomy between type 1 and type 2 cytokines is not absolute, however, because IFN-γ also can drive B cells to produce complement-fixing antibodies. In addition to providing B-cell help, type 2 cytokines such as IL-4 and IL-10 have anti-inflammatory properties and inhibit cell-mediated inflammatory responses. In vivo, most human CD4+ T cells do not display a rigid polarization to type 1 versus type 2, with a few infectious and allergic diseases representing notable exceptions. Rather, most CD4+ T lymphocytes produce both IFN-γ and IL-4.

Besides their conditioning effects on lymphocyte function, certain cytokines have robust effects on antigen-presenting cells. For example, IFN-γ upregulates the response of CD4+ and CD8+ T cells to antigen by enhancing the expression of MHC class II and class I structures on antigen-presenting cells. IFN-γ also can induce epithelial and fibroblastic cells to express MHC class (HLA-DR) structures on their cell surface, thereby becoming potential antigen-presenting cells for CD4+ cells (91).

Cytokine and cytokine networks cross-regulate each other in either positive or negative ways. Examples of positive effects include: (1) IL-2 induces production of IL-1α, IL-1β, IL-5, IL-6, IFN-γ, TNF-α, TNF-β, and granulocyte-macrophage colony-stimulating factor (92, 93); (2) TNF-α stimulates IL-1-production, and IL-1 stimulates IL-6 production (94); and (3) IL-1 and IL-6, or IL-2 and IL-6, in combination have potent synergistic effects on T cells and B-cell function (95–97). Examples of negative effects include: (1) IFN-γ inhibits IL-4 production, and vice versa; (2) IL-10 downregulates IL-2, IL-12, TNF-α, IFN-γ, and TGF-β (86, 99–100); and (3) IFN-γ and TGF-β inhibit IL-1 production (94). An important feedback regulatory circuit in the inflammatory response involves IL-1 via IL-6 in stimulating the release of glucocorticoid hormones, which in turn downregulate cytokine production (101).

The net effect of a given cytokine depends on the composition and the maturation state of T cells in the immediate environment. As an example, while IL-2 enhances the growth and differentiation of B cells in addition to their effects on T cells (94), IL-2 also has an important role in T-suppressor cell development (102). Also, the direct effect of IFN-γ on TNF-α produced by a CD4+ T-helper cell will be to facilitate B-cell differentiation. However, if T suppressor cells are able to interact with CD4+ cells, these cytokines may have the opposite effect on antibody production. In addition, while IL-4 is a B-cell growth factor, this cytokine appears to facilitate tolerance induction (103), which is an effect that can be abrogated by anti-IL-4 antibody (104).

TGF-β is a multifunctional cytokine with diverse effects on T-cell proliferation and helper activity (105). TGF-β promotes the growth of immature cells and inhibits differentiated cells (106). TGF-β generally downregulates B-cell function (107, 108), except for IgA production, and recently has been shown to be a critical costimulatory factor for the generation of CD8+ T-suppressor cells (109). It is important to emphasize that although most cells have the capacity to produce this cytokine, it is secreted as a latent complex. Only certain cells, either by themselves or when interacting with others, have the capacity to convert latent TGF-β to its active form. Macrophages and NK cells have this capacity, but T cells do not (86).

Cytokine Effects on T Lymphocytes in SLE

Cytokine Production and Responsiveness

In the following discussion, it is important to distinguish the properties of freshly isolated SLE mononuclear cells from those of cells that are stimulated in vitro. The former presumably reflect the activities of mononuclear cells in vivo, whereas observed defects of in vitro–stimulated cells may be explained by the refractory nature of in vivo–activated cells to further stimulation.

There are important technical considerations here. First, human studies generally are limited to peripheral blood cells for the assessment of cytokine production. Therefore, these cells may not faithfully reflect events in lymphoid tissues, the actual site of antibody production. Second, because most cytokines act at short distances, cytokine values in serum or plasma may not reflect locally high (and biologically important) concentrations produced in lymphoid tissues. Moreover, cytokines in the serum may be bound by proteins or complexed to soluble receptors or autoantibodies, which may affect clearance. Third, although levels of cytokines that are spontaneously released into cul-

Table 10.4. Cytokine Production in Patients With Active SLE

Cytokine	Spontaneous Release	After Stimulation of PBMC in Vitro	Serum Level
Type 1			
IL-2	low	decreased	increased
IFNγ	low	decreased	increased
IL-12	low	decreased	not known
Type 2			
IL-4	low	decreased	increased or normal
IL-6	high	not known	increased
IL-10	high	increased	increased
Other			
IL-1	increased	decreased	not known
TNFα	low	decreased	normal or increased
TGFβ	normal	active form decreased	normal

ture supernatants are readily comprehended, data obtained following mitogenic stimulation are more difficult to interpret (discussed later). Fourth, some investigators have studied cytokine mRNA synthesis, but these values do not always correlate with production of the secreted product. Fortunately, techniques to measure cytokine production by single cells have become available and been employed for use in human SLE. Cytokine production in SLE is summarized in Table 10.4.

Type 1 cytokines

As might be predicted from the well-described defects of impaired cellular immunity in SLE (6–8), production of IL-2, IFN, and IL-12 are decreased.

IL-2

CD4+ lymphocytes are the principal producers of IL-2. CD8+ cells generally are poor producers of IL-2 in response to antigens or mitogens, but they do generate substantial amounts of this cytokine when phorbol esters are added to the cell cultures (110, 111). CD3+ DN cells also produce IL-2 in response to mitogenic stimulation, but to a lesser extent than CD4+ cells do (112).

Spontaneous production of IL-2 by human T cells is very low, but the number of single cells producing this cytokine can be measured. Decreased values in subjects with both active and inactive SLE have been reported by workers using the enzyme-linked immune spot (ELISPOT) technique (113). IL-2 activity in culture supernatants of mitogen-stimulated peripheral blood mononuclear cells (PBMCs) also is decreased in SLE, although there is considerable heterogeneity within groups (114–125). This decrease truly reflects diminished production and not increased passive absorption of IL-2 produced by activated mononuclear cells (118). Decreased IL-2 activity is found in patients with active as well as inactive SLE (117) and in relatives of these patients (126). A recent study quantifying IL-2-producing lymphocytes following mitogen stimulation revealed a decrease that correlated with disease activity (127). Thus, in human SLE, there may be an inherited predisposition to low IL-2 production, but this trait is intensified with the onset of active disease.

Several mechanisms have been proposed to explain decreased IL-2 production by mitogen-stimulated cells in SLE. These include: (1) decreased numbers of IL-2-producer cells, (2) dysfunctional IL-2-producer cells, and (3) accessory cell defects or inhibitory serum factors. Although CD4+ cells frequently are decreased in number during active SLE (discussed earlier), decreased IL-2 production in patients with normal percentages of CD4+ cells has been documented (120).

Most workers agree that decreased IL-2 production is not the result of some intrinsic defect in the IL-2-producer cell. Three nonmutually exclusive mechanisms may be operative. IL-2 production by CD4+ cells may be inhibited by other lymphocyte subsets. Studies from our laboratory revealed that removal of radiosensitive CD8+ cells normalizes IL-2 production in SLE, and the suppressor cells were identified as being activated (HLA-DR+) CD8+ T or NK cells (128–130). A partially characterized suppressor factor that is produced by CD8+ cells could substitute for intact cells (131). The activity of these regulatory cells very likely might reflect a normal feedback regulatory mechanism to downregulate IL-2 that is produced by chronically stimulated, autoreactive T cells (discussed later).

A second mechanism to explain the decreased in vitro IL-2 production in SLE deals with the increased numbers of activated T cells in SLE (discussed earlier). Recently activated T cells are refractory to further stimulation. Indeed, resting SLE PBMCs for 2 or 3 days before stimulating these cells with phytohemagglutinin (PHA) plus phorbol ester normalized IL-2 production (118). Others have reported that the decreased IL-2 production correlated with increased surface expression of the MHC class II marker, HLA-DP; after culturing SLE lymphocytes, decreased numbers of HLA-DP+ cells correlated with increased IL-2 production (115). In contrast, two other groups also have reported that the addition of phorbol esters to PHA could correct the IL-2 defect in SLE (114, 120). Phorbol esters directly activate PKC and apparently bypass the refractoriness of activated SLE T cells.

A third possibility is that decreased IL-2 production may result from inadequate costimulation following contact with antigen-presenting cells. One group has reported an antigen-presenting cell defect in approximately one-half of the patients studied (125). It has been reported that SLE T cells can respond normally to accessory cells transfected with B7 (132), and very recently it has been documented that B7 upregulation (CD80 and CD86) on SLE accessory cells is diminished (132a, 132b).

A fourth mechanism involves serum factors. Antibodies in SLE serum have been described that inhibit IL-2 production by normal cells (133). Conversely, the levels of IL-2-inhibiting activity that normally are present in human

sera are decreased in SLE (134, 135). (Other serum inhibitors of T-cell function are described later.)

Although the numbers of IL-2-producing T cells circulating in the blood of patients with SLE are decreased, IL-2 nonetheless may be playing an important biologic role in SLE. First, increased levels of IL-2 in the serum of patients with SLE have been reported (136), Second, increased IL-2 production by SLE PBMCs cultured at low cell densities has been documented (137). Third, IL-2 mRNA transcripts can be detected in unstimulated PBMCs only from patients with SLE, but not from healthy controls or patients with tuberculosis (138). Fourth, anti-IL-2 antibodies markedly decreased spontaneous immunoglobulin production by SLE B cells (139).

Responsiveness to IL-2

The lymphocyte response to IL-2 following mitogenic stimulation is decreased in SLE (116, 140, 141), although not all patients demonstrate this abnormality (123). This defect appears to correlate with disease activity. In a recent longitudinal study, the decreased proliferative response to IL-2 normalized within 6 months after therapy, but 18 months were needed for the expression of high-affinity IL-2 receptors to become normal (127).

IL-2 receptors are comprised of a 55-kd α chain (CD25), a 70- to 75-kd β chain, and a 64-kd γ chain. Lymphocytes may express the α or chain either separately or together as a high-avidity IL-2-receptor. Although freshly isolated T cells from patients with active SLE may have increased α-chain expression, the β chain is not increased (142). Moreover, in response to mitogenic stimulation, there is less upregulation of both the α and β chains (140, 142, 143), predominantly in CD4+ cells (121, 143). Information concerning the γ chain is not yet available.

Decreased IL-2-receptor expression also may reflect a regulatory defect. The precursor frequencies of IL-2-responsive cells increased after "resting" them for 24 hours before mitogenic stimulation (122). The addition of IL-2 or IFN-γ to SLE lymphocytes partially corrects the defect (144–146). Of interest, although T cells are hyporesponsive, B cells in SLE show increased responsiveness to IL-2 (147).

IFNs

The role of interferons in the pathogenesis of human SLE is not clear. Several mouse models of SLE show clear evidence of increased IFN-γ production (113). In addition to facilitating cell-mediated immunity, both IFN-γ and IL-2 augment B-cell maturation (148). IFN-γ is an IgG switch factor that is important in the generation of complement-fixing antibodies. Patients with SLE characteristically have high levels of complement-fixing antibodies, and many have complement-fixing anti-double-stranded DNA (anti-dsDNA) antibodies, which are especially pathogenic. IFN-γ and IL-2 have been reported to enhance spontaneous IgG production by purified B cells from patients with SLE (149). Moreover, although IFN-γ inhibits both T- and B-cell proliferation in healthy subjects (150), this inhibition of B-cell proliferation was not observed in SLE (151). One group reported that the addition of IFN-γ to unseparated PBMCs decreased both total IgG and anti-DNA antibody production in SLE (152). In our laboratory, we have not been able to reproduce this phenomenon consistently.

IFNs may exacerbate, and even precipitate, human SLE, as has been reported in mice. Administration of IFN-α to patients with hematologic malignancies also has led to the appearance of autoantibodies and even clinical SLE (153, 154). Administration of IFN-γ to a patient with presumed rheumatoid arthritis exacerbated SLE (155, 156). Moreover, IFN-α has been implicated as a pathogenetic factor in lupus central nervous system (CNS) disease as well, in that a strong correlation has been reported between levels of IFN-α in the cerebrospinal fluid (CSF) and lupus CNS disease (157).

While serum levels of IFNs are increased in SLE, both spontaneous and mitogen-induced levels of IFN-γ appear to be decreased. The number of IFN-γ-producing cells spontaneously producing this cytokine is decreased in SLE, and this abnormality is more severe in patients with active disease (158). Others have reported that production of IFN-γ by mitogen-stimulated PBMCs usually is decreased in SLE (159–161). We recently investigated cytokine production in lymphocytes from patients at the time of diagnosis before treatment. Spontaneous production of IFN-γ was undetectable, and PHA-induced IFN-γ was significantly decreased (162). CD8+ cells appeared to be the predominant source of IFN-γ, because depletion of this subset markedly reduced production of this cytokine. Decreased in vitro production of IFN-γ correlated well with decreased NK cell activity (159). Like the IL-2 abnormality described earlier, addition of phorbol ester to the cultures reversed the defect (160, 163).

Serum levels of IFN-γ are increased in SLE, but these levels do not correlate with clinical activity (164, 165). Anti-IFN antibodies have been described in the serum of patients with SLE (166), which makes serum IFN-γ levels difficult to interpret. Serum levels of an acid-labile IFN-α are increased in SLE (167), and these levels correlate with disease activity (168–171). The acid lability of IFN-α in SLE is caused by a serum factor rather than being a reflection of an unusual IFN (172).

Thus, evidence gained from patients that supports a role for IFNs in the pathogenesis of SLE is equivocal at best. One way of explaining this paradox is to suggest that IFN-γ is important at the initiation of the disease but not as important in perpetuation. Again, one must caution that the observations in humans were made from studies of blood lymphocytes. Further confirmation is needed through studies of other lymphoid organs.

IL-12

IL-12 has emerged as a cytokine with a crucial role in host defense, especially against intracellular organisms. It conditions naive T cells to become effectors of cell-mediated

immunity (173). Studies in our laboratory (performed in collaboration with Dr. Giorgio Trinchieri) have revealed significantly decreased IL-12 production by mitogen-stimulated lymphocytes and monocytes in patients with new-onset SLE (162). Notwithstanding its potent effect on cell-mediated immunity, IL-12 can have the opposite effect on memory T cells. IL-12 also can provide B-cell help for complement-fixing antibodies (174). In fact, it is the most potent cytokine to costimulate IL-2-dependent B-cell immunoglobulin secretion (175). Thus, the effect of exogenous IL-12 on T-cell function in SLE is difficult to predict.

Type 2 Cytokines

There is evidence for an increased production of some type 2 cytokines in SLE, but one must emphasize that T cells may not be the principal source of these cytokines.

IL-4

In contrast to the substantial body of information regarding IL-2 and IFN-γ in SLE, much less information is available concerning IL-4. In our laboratory, we have not found IL-4 mRNA transcripts to be increased in freshly prepared lymphocytes; mitogen-induced IL-4 levels are normal and serum IL-4 levels not increased (136). Others also have not observed increased *IL-4* gene expression (176), but one group has reported increased serum levels of IL-4 (177). The failure of most investigators to find increased IL-4 production is not surprising, because in humans, this cytokine is elevated only in parasitic and allergic diseases that are associated with high levels of IgE (178, 179).

IL-5

This cytokine has not been investigated thoroughly in human SLE. Of interest, NK cells can produce this cytokine (176), and it has recently been reported that NK cells also have the capacity to induce resting T cells to become immunoglobulin-secreting cells (180).

IL-6

There is considerable evidence that IL-6 supports B-cell hyperactivity in SLE. Cultured SLE PBMCs spontaneously release increased amounts of this cytokine (181), and neutralizing anti-IL-6 antibodies decrease immunoglobulin production (176). T cells, B cells, and macrophages have been claimed as being the source of this cytokine (176, 182–186). Recently, increased numbers of IL-6-secreting cells were documented in SLE; analysis of single cells revealed that macrophages were the principal source (158).

One group has suggested that levels of IL-6 correlate with disease activity (187). Others, however, have not been able to document a correlation between in vitro levels of IL-6 and immunoglobulin production (185), and in a retrospective study, IL-6 levels and exacerbations of disease did not correlate (188). Although IL-6 also can be detected in the CSF, levels of this cytokine did not correlate with CNS disease in one study (157).

In addition to SLE, high serum IL-6 concentrations are found in a wide variety of conditions, including bacterial infections, burns, and alcoholic cirrhosis (189). In these diseases, IL-6 stimulates the liver to produce the acute phase–reactant, C-reactive protein. This protein, however, usually is not increased in active SLE.

Increased IL-6 production in SLE conceivably could be a consequence of autoimmunity. The principal nuclear autoantigens are derived from nucleosomes (i.e., structures that are the product of cells undergoing apoptosis). It has been reported that exposure of SLE PBMCs to ultraviolet light induces keratinocytes in the skin to undergo apoptosis (190). Others have reported that nucleosomes induce the spleen of lupus mice to produce IL-6 (191), and in humans, one group has reported that exposure of lupus PBMCs to light induces IL-6 production (192). Because apoptotic cells generally are phagocytosed by macrophages, it is not inconceivable that following exposure to sunlight, IL-6 could be produced by macrophages as a consequence of the phagocytosis of nucleosomal autoantigens. These cells also could process these autoantigens for presentation to autoreactive T cells.

Responsiveness to IL-6

Studies with IL-6 have provided evidence of a B-cell abnormality is SLE. Although low-density B cells from healthy subjects did not respond to this cytokine, low-density B cells from patients with active SLE directly differentiated into immunoglobulin-secreting cells without an additional costimulatory signal (193). While freshly isolated B cells from normal individuals do not spontaneously express IL-6 receptors, freshly isolated B cells from patients with SLE do express these receptors, which explains their responsiveness to IL-6 (194, 195).

IL-10

Spontaneous production of IL-10 is increased in both murine and human SLE, and there is a strong possibility that elevated levels of this cytokine contributes to the initiation and perpetuation of this disease. In human SLE, the numbers of IL-10-producing mononuclear cells are increased (113, 158), IL-10 mRNA synthesis in PBMCs is increased (196), and IL-10 secretion into culture supernatants is increased in short-term cultures of PBMC (162, 197). One group reported that both B cells and monocytes were the principal sources of IL-10 (197), while two other groups attributed this property to monocytes alone (113, 158, 162). Although T cells also can produce this cytokine, IL-10 produced by non–T cells appears to predominate. Serum levels of IL-10 are increased in SLE, which may correlate with disease activity (198).

IL-10 production is increased not only in SLE but in chronic infections (199) and acquired immunodeficiency syndrome (200) as well. In each of these diseases, this increase is presumably a feedback response to chronic im-

mune stimulation. Because of the inhibitory effect of IL-10 on IL-2, IFN-γ, IL-12, and TNF-α (98–100), this cytokine may be responsible for defects in cell-mediated immunity in patients with SLE and these other chronic inflammatory diseases.

In addition to this critical role in cell-mediated immunity, studies from our laboratory indicate that IL-2 as well as TNF-α and TGF-β are involved in the generation of lymphocytes that downregulate antibody production. We also have documented downregulation of TGF-β by IL-10 (86). Thus, elevated levels of IL-10 not only inhibit cell-mediated immunity but also may interfere with the critical regulatory circuit that is needed to terminate autoantibody production in SLE.

In mice, the administration of anti-IL-10 to NZB/NZW F1 mice greatly delayed the onset of SLE (201). As stated earlier, IL-10 downregulates TNF-α production. Of significant interest, it was the upregulation of TNF-α that followed antagonism of IL-10 that was essential in delaying the onset of SLE. In human SLE, addition of IL-10 to SLE PBMCs markedly reduces spontaneous anti-DNA production (202).

Other Cytokines

IL-1

Increased spontaneous release of IL-1 from SLE monocytes has been reported by several groups (184, 203–205), with one exception (206). In one study, increased release of IL-1α and IL-1β correlated with serum antibodies to ribonucleoprotein (203). In addition to monocytes, B cells can produce IL-1 as well as IL-6. It has been reported that IL-1 and IL-6 that are produced by SLE B cells sustain B-cell activity in an autocrine fashion (184, 192, 207), although others have reported that T-cell help is essential (19, 20, 139, 208).

In contrast to the increased spontaneous release of IL-1, the ability of monocytes or adherent cells to produce detectable IL-1 after stimulation is decreased in most patients with active disease (206, 209–212). In our laboratory, we found that decreased in vitro IL-1 production in SLE could be reversed by indomethacin, suggesting that prostaglandins might be responsible for decreased IL-1 production (213). Increased prostaglandin production by SLE monocytes has indeed been reported in SLE (211, 214), but this issue is not yet settled. Decreased IL-1 activity in vitro can be explained not just by defective synthesis but by IL-1-receptor antagonists as well. Of note, monocytes that are stimulated by immune complexes produce an IL-1-receptor antagonist (215), so SLE monocytes, having been exposed in vivo to circulating immune complexes, may be primed for the production of IL-1-receptor antagonist.

TNF-α

In humans and the NZB/NZW (B/W) mouse model of SLE, phenotypic polymorphism in TNF-α production appears to contribute to disease pathogenesis. Both the human and mouse form of the disease show a strong association with specific alleles of MHC gene products. TNF-α production by mouse macrophages in B/W mice is decreased, and the administration of recombinant TNF-α has an ameliorating effect on the development of nephritis (216, 217). TNF-α also has peculiar effects on human SLE B cells. While this cytokine is a growth factor in normal individuals, it inhibits B-cell proliferation and spontaneous production of IgM in patients with SLE (218).

Several groups, including our laboratory, have reported that in vitro production of TNF-α by stimulated PBMCs is decreased in human SLE (162, 210, 217, 218, 219). Production of TNF-α by both mitogen-stimulated macrophages and lymphocytes was decreased (162). In response to mitogenic stimulation, SLE patients with MHC class II antigens HLA-DR2 and DQw1 produce low levels of TNF-α, a phenotype that is associated with lupus nephritis (217). One group has reported that serum levels of TNF-α in SLE are normal or increased (220).

The mechanism of action of TNF-α in SLE is unclear. Although TNF-α protects B/W mice from renal disease, this therapy does not decrease the titers of anti-DNA antibodies (216). Moreover, treatment with low-dose TNF-α accelerates renal disease and the mortality rate (221). By contrast, the protective effect of anti-IL-10 in B/W mice is mediated by TNF-α. Administration of both anti-IL-10 and anti-TNF-α block the effects of antagonizing IL-10 (201).

Although TNF-α may be protective during initiation of SLE, this cytokine may have the opposite effect at the sites of inflammation. Both IL-1 and TNF-α have been implicated in the pathogenesis of lupus nephritis (221). Increased *IL-1β* and *TNF-α* gene expression have been detected in the kidneys of mice with lupus nephritis. Unstimulated, isolated glomeruli from mice with autoimmune lupus nephritis, but not control glomeruli, release TNF-α (222).

TGF-β

Recent analysis of TGF-β1 knockout mice (i.e., the mice produce no TGF-β1) has revealed striking evidence of autoimmunity similar to that in SLE. The sera of these mice contain elevated levels of predominantly IgG antibodies to single-stranded DNA (ssDNA), dsDNA, Sm, and ribonucleoprotein. Moreover, deposits were detected in the renal glomeruli of these TGF-β knockout mice (223, 224). Another group has documented that the introduction of *TGFβ* genes into MRL/lpr mice, by injecting plasmids containing TGF-β constructs into skeletal muscle, decreased autoantibody production (225).

The finding that active TGF-β is an important cofactor in the induction of T-suppressor cell activity may be a significant advance in understanding the regulation of antibody production, and it offers a new approach to elucidating the suppressor-cell defect in SLE. Significantly, we have found that in response to stimulation, the production of active TGF-β is decreased in SLE (86). Even so, the presence of a least some of this cytokine may attenuate B-cell function. The addition of anti-TGF-β antibodies to SLE

PBMCs resulted in increased spontaneous immunoglobulin synthesis (226, 227). In our laboratory, we also have found that TNF-α can upregulate the conversion of latent to active TGF-β (86). Therefore, this effect of TNF-α could contribute to the generation of T-suppressor cells.

Immunoregulatory Abnormalities in SLE

Percentage and Absolute Numbers of T-cell Subsets

Decreased numbers of T, B, and NK cells is a common manifestation of active SLE (228–233). Most patients with active SLE have total lymphocyte counts of less than 1000 cells/mm^3. Because of the relative decrease of lymphocytes in SLE in comparison to monocytes, the percentage of CD3+ T cells often is decreased in mononuclear cells preparations. The apparent percentage of T cells may be further decreased by the contamination of immature granulocytes that co-purify with mononuclear cells in patients with active disease.

Within the context of T-cell lymphopenia, certain T-cell subsets may be affected more than others in SLE. Early reports indicated a relative decrease in CD8+ cells in SLE (234, 235). One group indicated that patients with sicca syndrome, CNS disease, lung disease, and muscle disease exhibit increased CD4:CD8 ratios (236). Other studies have indicated that the relative percentage of CD8+ cells is either normal or increased, and that CD4+ cells often are decreased in active SLE (237, 238). In such cases, the decrease in CD4+ cells results in an abnormally low CD4:CD8 ratio, a finding that frequently is observed in patients with severe lupus nephritis (236, 239). Corticosteroid therapy preferentially decreases CD4+ cells and thus decreases the CD4:CD8 ratio (237). Decreased CD4+ cells correlate with antilymphocyte antibodies (ALAs) that are specifically reactive against this T-cell subset (240–242), and a strong relationship exists between high titers of ALAs, lymphopenia, and disease activity (228, 243–249). Within the CD4+ and CD8+ T-cell subsets, CD28+ cells are decreased in SLE (250).

In addition to alterations in the number or percentage of CD4+ cells, we reported an association between SLE and expression of a genetically determined variant of the CD4+ molecule in Jamaican black individuals (251, 252). Whether expression of this variant CD4 molecule truly predisposes certain individuals to develop SLE or simply acts as a marker for some other SLE-predisposing factor remains unknown at present.

CD4- CD8- (D uble-negative) T Cells in SLE

In addition to CD4+ and CD8+ T cells, there are small numbers of T cells that express neither CD4 nor CD8. These have been called *CD3+ double-negative (DN) cells* (112) and consist of two principal subsets. Two-thirds of these cells express TCRs that are comprised of γ and δ chains, and one-third bear α and β TCR chains (253, 254). Because CD3+ DN cells may develop outside the thymus (255), autoreactive DN cells may escape thymic deletion. Both $\alpha\beta$ CD3+ DN cells and $\gamma\delta$ CD3+ DN cells can provide help for anti-DNA antibody production (256), and $\alpha\beta$ CD3+ DN and $\gamma\delta$ cells are increased in patients with active SLE (123, 257).

Naive and Memory T Lymphocyte Subsets

CD4+ T cells with the naive phenotype (i.e., CD45RA+) were reported to be decreased in SLE (258–260). Because serum from patients with SLE contain autoantibodies against CD45RA, it was suggested that this subset, which has suppressor–inducer activity, was deleted (261, 262). Rather than a loss of lymphocytes, however, decreased numbers of CD45RA+ cells and a corresponding increase in CD45RA- cells likely reflect the maturation of T cells from the naive to the memory or activated state (37–40). Increased numbers of CD45RO+ T cells reflects increased T cell activation, which is a characteristic feature of SLE. At least some of these memory cells, which are more easily stimulated than naive cells, have the capacity to provide B-cell help for specific nuclear autoantigens (discussed later). Fortunately, antigen-specific suppressor–inducer cells also are derived from the CD45R0+ or memory-cell phenotype (263), which may counterbalance the autoantibody-promoting proclivity of helper-memory T cells.

Evidence of Previous Activation In Vivo

Blood lymphocytes isolated from patients with active SLE exhibit signs of previous in vivo activation. Examples of this include increased expression of MHC class II molecules, increased IL-2-receptor expression, the release of soluble IL-2-receptor and TNF receptors into the serum, and increased frequency of circulating T cells having undergone somatic mutation (264, 265) (Table 10.5). Activated, but not resting, T cells express HLA-DR on their cell surfaces, and as much as 20% of T cells from subjects with active SLE are HLA-DR positive. Some investigators have reported increased CD4+ DR+ cells (266), and others have reported an increase in CD8+ DR+ cells (267). We and others have reported an increase in both CD4+ DR+ and CD8+ DR+ cells (117, 268). Surface expression of HLA-DP also is increased in SLE (115). In addition, patients with active SLE have increased expression of proliferating cell nuclear antigen (i.e., cyclin) (269), a finding that is consistent with the observation of increased numbers of spontaneously proliferating lymphocytes in SLE (270).

Studies using radiolabeled IL-2 have revealed significantly increased levels of cell surface IL-2 receptor in patients with active disease compared to those with inactive disease (147). Other studies using anti-IL-2 monoclonal

Table 10.5. Evidenc f *In Vivo* T Cell Activationin Subjects With Active SLE

1. Increased cell surface expression in unstimulated T cells of MHC class II (HLA-DR, -DP) structures, and, to a lesser extent, interleukin-2 receptor expression and TLiSA1.
2. Increased expression of proliferating cell nuclear antigen in unstimulated T cells.
3. Increased levels of mRNA transcripts for interleukin-2 in unstimulated T cells.
4. Increased serum levels of interleukin-2, soluble interleukin-2 receptors and interferon-γ, and tumor necrosis factor alpha (p55 and p75).
5. Increased frequency of circulating T cells bearing somatic mutations in the HGPRT gene (the mutation rate is a function of cell division).

antibodies that recognize the p55 component of IL-2 receptor have indicated that the increase in IL-2-receptor expression is more modest than the increase in HLA-DR+ cells in patients with active SLE (117, 271). This probably is because IL-2 receptors tend to disappear from the cell surface after chronic stimulation of lymphocytes.

Serum-soluble IL-2-receptor levels also are increased in SLE, and some investigators have reported a correlation with disease activity (272, 273–278). Soluble TNF receptors also are increased in SLE. Concentration of both the p55 (i.e., type I) and p75 (i.e., type II) soluble receptors were significantly higher in SLE, and these values correlated with clinical activity (279). The release of sIL-2 receptor and sTNF receptor appear to be regulated independently (280). Soluble CD8 levels also are increased in SLE (Linker), but two groups were unable to find a correlation of this marker with clinical activity (277, 278).

Antigen Recognition by T Cells

Tolerance Induction

Defects in tolerance induction have been reported in murine SLE (281). Generation of the T-cell repertoire and deletion by negative selection appear to be intact (282, 283), so this defect does not appear to be in the intrathymic T-cell development. In contrast, several groups have reported defects in peripheral tolerance following challenge with superantigens (284–286), although not all groups agree (283). Mice with a genetic defect in the apoptosis-promoting gene *fas* appear to have a defect in peripheral tolerance that is associated with aging (286).

Although analogous studies of tolerance induction in humans cannot be performed, structures that are involved programmed cell death have been studied in SLE. Fas-mediated cytotoxicity represents a major pathway leading to cell death (288–291). This is an important mechanism in peripheral tolerance. Mice that are homozygous for either *lpr*, a mutation in the *fas* gene (292), or for *gld*, a point mutation resulting in defective or absent Fas ligand expression (293–295), develop generalized lymphadenopathy in association with lupus-like features (296). These mice have impaired deletion of self-reactive B cells and expansion of autoreactive T cells (284, 297). Conversely, MRL-*lpr/lpr* mice that are transgenic for the intact *fas* gene under the control of a T cell–specific CD2 promoter and enhancer do not develop the lymphadenopathy, glomerulonephritis, or clinical autoimmunity that their nontransgenic littermates do (298). Although Fas expression is not decreased in human SLE and actually may be increased (299–301), the potential ramifications of the observations in murine *lpr* and *gld* mice for human disease have been highlighted by two recent reports that describe an association in *humans* between *fas* mutations and clinical autoimmunity and/or lymphadenopathy (302, 303). Moreover, soluble Fas protein, which can inhibit apoptosis of stimulated cells under appropriate conditions, has been reported to be elevated in the serum of many patients with SLE (304), although this finding has recently been challenged (305, 306).

Other structures may prevent apoptosis. Enforced expression of *bcl2* leads to enhanced cell survival and growth (307–309). Mice that are transgenic for *bcl2* under the control of an immunoglobulin μ-chain enhancer not only develop elevated numbers of B cells and serum immunoglobulin levels but also spontaneously develop autoantibodies and immune-complex glomerulonephritis (310). Indeed, *bcl2* expression has been reported to be elevated in freshly isolated SLE peripheral blood T cells (301, 311, 312) and B cells (311), again supporting the notion that the impaired demise of such cells may be a factor in the development of clinical autoimmunity.

Antigen Specificities of Self-reactive T Cells

As discussed, T-cell recognition of and response to both foreign and self-antigens is determined by the class I and II MHC gene products of the host. T-cell cytokine production and subsequent helper activity therefore is influenced by the expression of MHC alleles on antigen-presenting cells. For example, expression of HLA-DR3 is associated with decreased production of IL-1 and IL-2 (313); expression of HLA-DR2 and DQw1 correlates with elevated anti-dsDNA autoantibody titers, decreased production of TNF-α in vitro, and lupus nephritis (217); and expression of both HLA-DR3 and DQw2 correlates with detectable anti-Ro/SSA and anti-La/SSB antibodies (314, 315).

Because the recognition processes of T cells for self- and foreign antigens are similar, one must consider whether antigen-presenting cells in SLE aberrantly process self-antigens or whether there may be an increase in T cells that are capable of responding to self-peptides. Regarding the former possibility, abnormalities of SLE monocytes have been described. Depletion of monocytes decreased anti-

DNA antibody production in vitro, and adding the SLE monocytes back into cultures increased production of this autoantibody (316). Regarding the latter possibility, there is no evidence for the oligoclonal expansion of T cells in human SLE as manifested by restricted usage of T-cell antigen receptor variable-region genes (317, 318). There is a single report where restriction fragment length polymorphism studies revealed an association between one framework gene encoding the constant region of the TCR-α region and SLE (319).

Although T cells from patients with lupus generally are poorly reactive to mitogens and antigens, autoreactive T-cell lines and clones that can augment anti-DNA antibody production have been developed and characterized (320, 321). Murine T cell clones that are MHC class II restricted and provide B-cell help for IgG anti-DNA antibodies have also been described. One group found that these clones expressed $\alpha\beta$ TCR and produced IL-4, but not IL-2 or IFN-γ (320). Another group found that approximately one-half of these clones responded to nucleosomal antigens that contained cationic residues (321). The CDR3 loops of TCR β chains contained a recurrent motif of anionic residues, whereas the TCR α chains contained both anionic and cationic residues in their CDR3, suggesting that these pathogenic clones probably recognize autoantigens with epitopes of mixed charges (322).

Unlike the mice, almost all TCR$\alpha\beta$ clones derived from human SLE patients were CD4+; similar to the mice, the TCR expressed a recurrent motif of highly charged residues in their CDR3 loops. T-helper lines from four or five patients showed evidence of antigenic selection. There was a marked increase in the Vα 8 gene family as well as identical TCR α and/or β sequences. These clones responded to either charged chromosomal proteins or nucleosomal histone proteins presented by HLA-DR molecules (323).

T-cell Lines and Clones

Human T-cell clones generated from the PBMC of patients with SLE or mixed connective tissue were found to react against uridine-rich, RNA-small nuclear ribonucleoprotein antigen (snRNP) antigen. Similar clones, however, were produced from MHC genotype–matched normal controls. These were oligoclonal CD4+ TCR $\alpha\beta$ memory cells (324). Notwithstanding the impaired response of SLE T cells to soluble antigens, a proliferative response to a ribosomal P fusion protein recently has been reported (325).

In addition to recognizing cellular constituents, there also is evidence in mice that antigen-specific T-helper cells recognize determinants from the VH region of B cells, which produce anti-DNA antibodies. Immunization of B/W mice with either of three specific VH peptides increased anti-DNA levels, accelerated nephritis, and decreased survival. T cells that are immunized with these peptides produced either a TH1 or TH2 profile of cytokines, but adoptive transfer of either of these T cells accelerated disease (326). Others have induced SLE syndromes in mice by immunization with specific anti-DNA antibodies (11). These observations suggest that anti-idiotypic T-cell responses can enhance, and even initiate, SLE.

Another approach to identify previously activated autoreactive T cells in SLE has been to take advantage of the increased mutation rate of cells that have undergone frequent cell division in vivo. The frequency of these mutant T cells increases with the degree of immunologic stimulation, as reflected by the overall magnitude of disease, the number of flares, and the presence of photosensitive skin rash. Mutations were found in CD4+, CD8+, and the minor CD3+ CD4- CD8- populations. When these T cells were cloned, a substantial number were able to provide help for autologous B cells to produce anti-ssDNA (264, 265).

T-Lymphocyte Function in SLE

In the early 1970s, workers from several laboratories reported that patients with active SLE responded poorly to intradermal injected skin test antigens (6–8). This observation was followed by numerous reports of abnormal defects in the T-cell proliferative responses to mitogens (327–330), to soluble antigens (331), and to MHC class II antigens on both allogeneic (332–334) and autologous antigen-presenting cells (335–337). Generation of antigen-specific, cytolytic T cells also was found to be decreased (338, 339). A partial summary of T-cell functional defects is presented in Table 10.6.

In principle, T-cell functional defects could be explained by an inherent T-cell defect or by defects external to the abnormal T cell. In support of an inherent defect, impaired capping of membrane CD3, CD4, and CD8 following incubation with the corresponding monoclonal antibodies was noted in T cells from patients with SLE (340). This led to identification of a defect in the cAMP metabolism of CD4+ cells in SLE (341), and this defect has been documented in patients with inactive as well as active disease. Most recently, this same group described deficient type I PKA isozyme activity in SLE T lymphocytes (342). Although these findings suggest some role for an inherent T-cell defect in SLE, the principal pathogenic defects appear to involve those dealing with the way that antigen is presented to T cells and with the regulatory cells themselves. Each step leading to T-cell effector function is reviewed here.

Early Activation Events

Intuitively, T-cell effector function is the culmination of an ordered sequence of specific intracellular biochemical processes. Subtle alterations in these processes may lead to loss of or change in effector function. Several laboratories, including our own, have demonstrated *normal-to-enhanced* CD3/TCR–mediated proliferation of purified T cells in SLE (339, 344, 345), whereas CD3/TCR–mediated gen-

Table 10.6. T Lymphocyte Functional Activities In Vitro

Function	Activity
Proliferation	
mitogenic lectins	decreased or normal
anti-CD3	decreased or normal*
anti-CD2	decreased
soluble antigens	decreased
allogeneic mixed lymphocyte reaction	decreased
autologous mixed lymphocyte reaction	markedly decreased
response to interleukin 2	decreased or normal
Helper cell activity	
nonspecific	decreased or normal
antigen specific	decreased
Suppressor cell activity	
con A induced	decreased or normal
antigen specific	decreased
spontaneous inhibitors of IL-2 production	increased
Cytotoxic cell activity	
in response to allogeneic or xenogeneic antigens	decreased
in response to hapten-modified antigens	increased
in response to anti-CD3	decreased
in response to IL-2	decreased

*When isolated T cells are used instead of PBMC, the response to αCD3 is normal or increased.

eration of T-cell cytolytic activity in SLE was *subnormal* (235, 338, 346). This dissociation of *normal* T-cell proliferation from *subnormal* T-cell cytolytic activity in SLE strongly suggests that multiple chains of intracellular biochemical processes coexist in parallel. SLE T cells, on activation, may trigger one chain of intracellular events, leading to a normal response for a certain T-cell parameter, but also trigger another chain of intracellular events, leading to an abnormal response for a different T-cell parameter.

Despite the obvious importance of intracellular second messengers to T-cell function in SLE, relatively little is known regarding their levels, generation, or regulation in SLE. Impaired calcium responses to PHA and anti-CD3 monoclonal antibody in T cell–enriched populations with SLE have been reported (114), as have *increased* calcium responses to anti-CD3 monoclonal antibody (347). Reasons for these disparate results remain unclear at present, but they may reflect the inherent complexity of CD3/TCR–triggered calcium responses and the heterogeneity of patients with SLE who are available for study.

PKC activity in response to phorbol ester may be somewhat lower in SLE T cells than in normal T cells (348). Generation of intracellular cAMP levels in response to multiple stimuli is impaired in SLE PBMCs and T cell–enriched populations (348, 350), and PKA activity has been suggested to be abnormal in T cells from patients with active SLE when compared to T cells from either normal donors or patients with rheumatoid arthritis or Sjögren's syndrome (351).

The Proliferative Response to Soluble and Cell Surface Antigens

With the exception of one early report (352), there is general agreement that lymphocyte proliferation in response to soluble antigens is decreased in patients with active SLE (8, 331). In retrospect, the difference in findings is probably related to disease activity. The reasons why the T-cell proliferative response to soluble antigens in SLE is decreased to a greater extent than the response to mitogens are not well understood.

T-cell responsiveness to both allogeneic and autologous lymphocytes is decreased in SLE (144, 332–334, 353, 354). In the autologous mixed lymphocyte reaction (AMLR), CD4+ T lymphocytes recognize self-MHC class II antigens on non-T cells. They respond by secreting IL-2, which promotes the proliferation of IL-2-receptor–positive T cells. Considerable precaution must be taken in setting up the AMLR, because foreign antigens contained in fetal calf serum (used as culture growth factors) also can stimulate T cells to proliferate. However, with care, the AMLR can reflect a physiologic response that results in the induction of B-cell differentiation and the activation of T-suppressor cells (354). Impaired AMLR in SLE may be caused by the inability of SLE T cells to produce adequate amounts of IL-2 (144). In addition, naive (i.e., CD45RA+) CD4+ T cells, which proliferate in response to self-antigens, are decreased in SLE (258–260).

The Proliferative Response to Mitogens

Most investigators have reported decreased proliferative responses of SLE blood leukocytes or mononuclear cells in vitro to mitogenic lectins (i.e., PHA, concanavalin A [Con A], and pokeweed mitogen) (8, 327–329, 355–361). The significance of these observations is unclear, however, because observers have been unable to correlate decreased mitogenic activity with clinical activity. Moreover, several groups have reported normal responsiveness to mitogens (330, 360, 361).

These discrepant results could be attributed to differences in the patient populations that were studied, differing cell-preparation procedures, and differing culture conditions. Regarding the last possibility, factors that may explain decreased mitogenic reactivity include inhibitory monocytes (355), hypergammaglobulinemia (356), and inhibitory antibody and nonantibody serum components (362–364). Along these lines, studies conducted in our laboratory revealed that impaired mitogenesis in SLE was most easily demonstrated by comparing cells from patients

and control subjects cultured in a standard lot of human AB serum and in the presence of suboptimal doses of mitogens. Decreased responses were observed, especially in those patients who were anergic to skin-test antigens. Although depressed mitogenic reactivity did not correlate with clinical activity, the degree of serum suppression was positively correlated with disease activity, and the principal serum inhibitor was found in the IgG fraction (362).

In addition to mitogenic lectins, the proliferative responses to mitogenic anti-CD3 and anti-CD2 monoclonal antibodies have been examined. Although proliferation of unfractionated PBMCs to anti-CD3 monoclonal antibodies may be depressed in SLE (365), isolated T cells generally exhibit normal to increased responsiveness in SLE (339, 366, 367). Thus impaired proliferative responses of SLE PBMCs to anti-CD3 monoclonal antibodies appear to result from an abnormality in accessory (i.e., non-T) cells rather than from an inherent T-cell defect.

The proliferative response to anti-CD2 also is depressed because of multiple defects (368), and we have confirmed this observation in our laboratory. As was the case for anti-CD3, we documented an accessory cell defect in the majority of patients, because the defect disappeared following depletion of these cells. Although proliferation in response to anti-CD2 appeared to be exquisitely sensitive to prostaglandin E_2 (PGE_2), we were unable to document increased PGE_2 production by SLE monocytes. Most important, the addition of anti-CD28 also reversed the defect (369). Others have found that the costimulatory effect of anti-CD28 markedly enhanced the capacity of patients with active SLE lymphocytes to produce IL-2. (250). This defective proliferative response to anti-CD2 in SLE may be important, because we recently demonstrated that signaling through this pathway selectively triggers the TGF-β-dependent suppressor-cell pathway (86). Anti-CD2, but not anti-CD3, has this capacity as only the former stimulates NK cells (discussed later).

The markedly enhanced T-cell proliferative response to anti-CD3 and anti-CD2 following monocyte depletion suggests that T cell–accessory cell interactions are impaired in SLE. Several pairs of receptor/coreceptor pairs on T cells and accessory cells that are crucial to T-cell costimulation have been identified, including CD2/CD58 (LFA-3), CD11a (LFA-1)/CD54 (ICAM-1), and CD28 or CTLA-4/CD80 (B7.1) or CD86 (B7.2). Blockade with specific monoclonal antibody or soluble fusion proteins of the receptor/coreceptor interactions can inhibit T-cell proliferation, T cell–dependent B-cell differentiation, and/or induction of T-cell cytolytic activity (55, 370–378). At present, it is unclear whether the basis of the putative defect in T cell–accessory cell interactions can be attributed to decreased expression of any of these costimulatory molecules. Indeed, expression of CD11a and CD54 are *increased* in SLE (379, 380), and increased T-cell CD11a expression has been associated with the development of autoreactivity (380). CD80-delivered signals to SLE T cells do result in normal enhancement in anti-CD3-induced T-cell proliferation (381), but the role of CD86-delivered signals and actual expression of CD80 and CD86 on SLE accessory cells remains to be fully clarified.

T-helper C II Activity in SLE

Although there is considerable evidence of increased T-cell activation in vivo, T-helper cell activity in vitro induced by pokeweed mitogen is either decreased (16, 382) or normal (383, 384). T-helper cell activity induced by specific antigens is decreased in SLE. Unlike normal lymphocytes, SLE cells that are immunized in vitro with trinitrophenyl polyacrylamide beads were unable to generate antigen-specific, antibody-forming cells. SLE B cells responded when cocultured with normal T cells, but SLE T cells were unable to provide help for normal B cells (385). The ability of SLE T cells to support B-cell colony formation also is defective in SLE (386). Again, the failure of SLE T cells to respond normally to mitogens or antigens may be explained by the fact that in vivo–activated T cells respond poorly to subsequent in vitro stimulation. Alternatively, regulatory cells that are generated by chronic antigenic stimulation in vivo may inhibit T-cell activation in vitro (129). Importantly, the T-cell helper defect in SLE may not prevent the development of essential memory responses. Although primary antibody responses may be depressed, secondary responses are normal (387, 388).

T-suppressor Cell Activity

During the 1970s, assays to measure T-suppressor activity were developed (389), and numerous investigators reported a defect in SLE (390–406). Here, "suppressor" activity was generated in vitro by culturing mononuclear cells with Con A, and the effects of these activated cells on other lymphocytes were determined. A T-suppressor cell defect in first-degree relatives of patients with SLE was documented that correlated with increased levels of 16/6, which is a cross-reactive idiotype of monoclonal anti-DNA antibodies (407). This observation reinforced the notion of a genetic predisposition to SLE; however, the relevance of Con A–induced suppression to the regulation of antibody production in SLE has been seriously questioned, and so has the entire issue of "suppressor" cells.

Nonetheless, CD8+ and NK cells from patients with active SLE often are unable to downregulate polyclonal immunoglobulin synthesis (389, 139) and autoantibody production (20, 139). Previously, DNA-induced antibody synthesis was analyzed in a pair of identical twins who were discordant for SLE; only B cells from the SLE co-twin could produce anti-DNA antibodies. Addition of the SLE co-twin's T cells to her own B cells promoted anti-DNA antibody production induced by calf thymus DNA. On the other hand, T cells from the unaffected co-twin did not promote anti-DNA antibody synthesis unless CD8+ cells were depleted. This finding suggested that the healthy co-twin had anti-DNA–specific T-helper cells, but that they were kept nonfunctional by CD8+ suppressor cells (20).

Studies from our laboratory revealed the surprising ob-

servation that CD8+ DR+ T cells supported polyclonal IgG synthesis. Moreover, in the concentrations added, CD4+ cells by themselves were unable to sustain anti-DNA antibody production. The addition of CD8+ or NK cells to CD4+ cells was necessary to support autoantibody production (139). These observations point to dysregulation of both CD8+ and NK cells in SLE.

As described earlier, cross-talk between CD8+ and NK cells in healthy individuals induces the active form of TGF-β, which serves as a critical costimulatory factor for the generation of T-suppressor effector cells (109). Although levels of TGF-β appear to be normal in SLE following T-cell stimulation in vitro and in the serum, conversion of the latent complex to active cytokine is decreased in SLE. We also have preliminary data that the addition of recombinant IL-2 and TGF-β together to cultures containing CD8+ T cells can restore suppressive activity (Horwitz et al., Unpublished observations). These studies require confirmation.

T-cell Cytotoxic Activity

The importance of intact generation of T-cell cytolytic activity has long been appreciated by viral and tumor immunologists who recognized the central role of cytotoxic T lymphocytes (CTL) in ridding the host of infectious viruses and of incipient tumors. Besides the abnormalities in NK cell cytotoxic activity discussed later, abnormalities in T cell–dependent or –mediated cytolytic activity have been reported in SLE. These include impaired pokeweed mitogen–induced cytotoxicity (408), impaired generation of cytotoxic T cells against allogeneic or xenogeneic targets (338, 409), and impaired anti-CD3-driven cytolytic activity (339, 346). The latter reports may be especially important in that anti-CD3 monoclonal antibodies, which activate all T cells, could lead to *normal* T-cell proliferation in SLE despite *abnormal* T cell–mediated cytolytic activity. In monozygotic twins discordant for SLE, the defect in cytolytic activity is often detectable in the clinically healthy co-twins (287), suggesting that the CTC defect truly antedotes onset of clinical disease.

In a murine graft-versus-host (GVH) model, inoculation of (C5781/6[B6] × DBA/2[DBA])F_1 recipient mice with T cells from one parental strain (B6) resulted in an immunosuppressive GVH reaction with no clinical autoimmune features, whereas inoculation of recipient F_1 mice with T cells from the other parental strain (DBA) resulted in an immunostimulatory GVH with clinical features resembling SLE. In either case, infused parental CD+ T helper cells because activated, so differential activation of CD4+ T cells could *not* explain the dichotonous outcomes. Further analysis revealed that the number of anti-F_1 cytotoxic T-lymphocyte precursor cells (CTLp) was markedly lower in the SLE-like GVH reaction than in the non-SLE-like GVH reaction, and that elimination of CD8+ T cells (presumably containing the relevant CTLp) derived from parent A before inoculation of the F_1 recipients also resulted in an SLE-like response (410). Thus, based on this murine GVH model, the absence of an adequate *polyclonal* T cell–mediated cytolytic response may be an important contributing factor to the development of SLE.

Patients with SLE, never having received foreign tissues, obviously do not experience GVH reactions per se. Nevertheless, polyclonal T-cell activation leading to autoreactivity and help for autoantibody production could arise following exposure to environmental infectious agents. A compelling argument has been offered for the role of microbial superantigens (which, like anti-CD3 monoclonal antibodies, activate T cells via surface CD3/TCRs) in the triggering of polyclonal T-cell autoreactivity, which under the proper setting could result in SLE (411). Thus, the observed in vitro defect in anti-CD3-induced polyclonal T cell–mediated cytolytic activity may reflect similar in vivo defects in generating polyclonal T cell–mediated cytolytic activity, resulting in dysregulated polyclonal T-cell helper activity and predisposing to the development of SLE.

Importantly, as *lpr* mice age, NK1+ T and non-T cells (analogous to human CD56+ T and non-T cells) disappear concomitant with development of clinical autoimmunity. Treatment with anti-NK1 antibody of young mice prior to their manifesting clinical disease hastens development of autoimmunity, whereas adoptive transfer of NK1+ cells delays the onset of autoimmunity (412). These observations suggest that the continued presence and function of NK1+ (CD56+) T and/or non-T cells is integral to the prevention of clinical autoimmunity. Of note, in vitro anti-CD3-driven generation of and cytolytic function of CD56+ (T) cells are also frequently impaired in human SLE despite normal total T cell expansion (287). By analogy to the presumed role for NK1+ cells in mice in preventing autoimmunity, the defect in generation and cytolytic function in CD56+ (T) cells may play a predisposing and/or pathogenetic role in human SLE.

Serum Inhibitors of T-cell Function

SLE sera inhibit lymphocyte proliferation in response to mitogenic lectins (356, 362, 363), soluble antigens (242), and allogeneic (353, 413) as well as autologous MHC antigens (333, 414–417). These sera also block the generation of cytotoxic T cells (338) and interfere with antigen presentation by macrophages (418). Much of this inhibitory capacity can be ascribed to IgM and IgG antibodies, which react with various lymphocyte cell surface molecules. SLE ALAs react with activated lymphocytes more strongly than resting lymphocytes (242, 419, 420). IgG ALAs inhibit suppressor cell generation and activity (415, 421). In addition, IgG ALAs inhibit mitogen- and mixed lymphocyte reaction (MLR)-induced proliferation (353, 362, 363, 413, 415, 420, 421) and preferentially inhibit the T-cell response to soluble antigens (242).

Although initially reported only to react with T-suppressor cells (422, 423), ALAs react with both CD4+ and CD8+ cells (240, 424) and actually appear to react preferentially with CD4+ cells (241). Such autoantibodies may result in altered CD4:CD8 ratios, leading to altered im-

mune function. In addition, IgM autoantibodies that are reactive with the membrane tyrosine phosphatase CD45 molecule have been described in SLE (425, 426). These antibodies preferentially react with the high-molecular-weight CD45RA isoform that is expressed on naive T cells (29). Such autoantibodies may interfere with T-cell signal transduction. Autoantibodies against the MHC class I–associated beta$_2$-microglobulin (427) and MHC class II molecules (415) also have been described. Such autoantibodies could inhibit T-cell function by blocking cell-to-cell interactions.

The Role of T Cells in the Initiation of SLE

A proposed sequence of events leading to the various SLE syndromes are outlined in Fig. 10.7.

Genetic factors

Genetic factors predispose certain individuals to develop SLE. In mouse lupus, at least six chromosomal loci have been identified (428, 429). One of these genes is in the MHC on chromosome 17 in mice and chomosome 6 in humans. These genes shape the T-cell repertoire and regulate the antigens that are presented to T cells. Although the MHC class II gene products HLA-DR2/DQw1 and DR3 have been linked with increased susceptibility to certain SLE syndromes, the specific gene that is responsible for this susceptibility has not been defined as yet. In mice, there is evidence to suggest a role for specific MHC class I genes (430). MHC class III genes also are candidates, including the genes for C2, C4, and TNF-α. Individuals with deficiencies of early complement components have an increased susceptibility to SLE (430), which perhaps is related to an impaired ability to clear immune complexes from the circulation. Patients with lupus who possess HLA-DR2/DQw1 have low TNF-α production and increased susceptibility to develop nephritis within the first 5 years after diagnosis (217).

As stated earlier, CD8+ lymphocytes have an impaired ability to become killer cells in SLE. The observed in vitro defect in anti-CD3-driven CTL activity in SLE (339, 346) may reflect similar in vivo defects in generating polyclonal CTL activity, resulting in dysregulated polyclonal T-cell helper activity and predisposing to the development of SLE. Indeed, the CTL defect in SLE is independent both of disease activity and of immunosuppressive medications (346). Moreover, as discussed, in monozygotic twins who are discordant for SLE, the defect often is detectable in the clinically healthy co-twins (287), raising the possibility that the CTL defect in SLE may be inherited. These individuals may have an increased risk of developing SLE if they are exposed to one or more inciting environmental factors. Whether these putative inherited factors are MHC gene products remains to be determined.

Role of Infectious Agents

Infectious agents can act as the trigger factors to induce polyclonal B-cell activation and autoimmunity. A compelling argument for microbial superantigens has been offered in triggering polyclonal T-cell helper activity, which may result in SLE (413). Microbial superantigens, like anti-CD3 monoclonal antibodies, activate T cells via surface CD3/TCR. Certain bacteria such as staphylococci, streptococci, and mycoplasmas bear structures called "superantigens" that simultaneously bind to specific structures on the variable (V) region of the TCR β chain and to the class II MHC molecules of antigen-presenting B cells. Therefore, these structures bring CD4+ cells into close contact with B cells. Such bridging of T and B cells by microbial superantigens can induce polyclonal IgM and IgG formation. Moreover, specific autoantibodies may be produced if there also is concurrent crosslinking of the B-cell receptor by autoantigen (413).

Antibody production induced by T cell–dependent B-cell differentiation (380, 432) appears to be regulated by mechanisms involving the killing of B-cell targets by CD4+ and/or CD8+ T cells (433) and suppression by CD8+ cells (109). Moreover, as documented for HIV (433a) but likely also the case for other viruses, T cells can become potent, unrestricted helpers for immunoglobulin production following their infection with certain viruses and incorporation of the viral genomes. In either of these two scenarios, under *in vivo physiologic conditions*, T cells would be activated through *antigen-independent*.

In addition to triggering polyclonal T cell–dependent B-cell differentiation, persisting infectious organisms induce a chronic inflammatory reaction. This creates conditions that are suitable for a breakdown of self-tolerance and the induction of autoimmunity by three mechanisms. First, the adjuvant-like effects of the organisms persisting in the inflammatory exudate can stimulate lymphocytes and macrophages that are present to secrete cytokines such as IL-2. This potent T-cell growth factor has the capacity to convert anergic self-reactive T cells into T cells that are fully capable of responding to nuclear and cytoplasmic antigens. Second, these self-antigens would be immediately available for presentation to T cells. Macrophages in the inflammatory exudate will phagocytose dead cells, and both cytoplasmic and nuclear proteins from these dead cells will be degraded and some of the processed peptides complexed to MHC class II molecules for presentation to the self-reactive T cells. Third, regulatory cells that generally are capable of preventing autoimmunity become dysfunctional as a consequence of the sequelae of chronic inflammation.

In addition to infections, certain drugs are other environmental agents that can cause lupus-like syndromes. Some drugs are capable of converting anergic, autoreactive T cells to immunocompetent ones through a mechanism involving DNA methylation. Inhibitors of DNA methylation induce gene expression, and it has been reported that

drugs such as procainamide and hydralazine induce self-reactivity in cloned T-cell lines by this mechanism (380, 434, 435).

The Nature of Autoantigens in SLE

The antigen that is responsible for the initiation of SLE remains in doubt. Features of molecules that induce autoantibodies in SLE are their highly charged nature, such as RNA, DNA, or histones, or their highly repetitive nature, such as cell surface carbohydrates. Although SLE is characterized by anti-DNA antibodies, native mammalian DNA is a poor immunogen. Even purified denatured DNA that is complexed to an immunogenic carrier protein does not induce antibodies to native DNA (436, 437). Bacterial DNA, however, can induce anti-dsDNA antibodies in nonimmune mice (438), and DNA–protein complexes can trigger pathogenic anti-DNA antibodies in SLE. DNA that is bound to histone or complexed to other proteins is, in fact, a common target of autoantibodies in SLE (439, 440). Anti-DNA antibodies that are similar to those detected in human SLE have been raised in nonautoimmune mice immunized with a human DNA–protein complex that is present at high levels in the circulation of patients with SLE (441), and certain nucleoprotein fractions isolated from immunoblots also can stimulate SLE T cells (442).

There is increasing evidence that nucleosomes may be the fundamental immunogen (436). Conformational epitopes on native chromatin and the $(H2A\text{-}H2B)_2$-DNA subnucleosome induce specific antibodies, which then spread in a stepwise manner to include IgG antihistone and antinative DNA activates (443, 444), which may be complement fixing. Nucleosomes typically express cationic residues that bind to complementary-charged domains of TCR that are expressed by autoreactive T cells (321, 322). Thus, the epitopes that T cells recognize are peptide fragments of the proteins that are complexed with DNA or histones in nucleosomes.

Drugs also can induce lupus syndromes by causing DNA damage and releasing altered nucleosomes (445) in addition to inhibiting DNA methylation as described earlier (380, 434, 435). Studies of apoptotic keratinocytes have revealed blebs containing nucleosomes and spliceosomes which bear most of the predominant SLE autoantigens (190, 191). These structures are subject to oxidative modification. Following phagocytosis and processing by antigen-presenting cells, the altered epitopes may be rendered strongly immunogenic for nontolerant CD4+ T cells.

B Cells as Autoantigen-presenting C lls in SLE

Persistent T-cell activation and/or polyclonal B-cell activation and impaired regulation of antibody production (discussed later) set the stage for the breakdown of T-cell tolerance and generalized autoimmunity. Because B cells that are reactive to self-nuclear and certain cytoplasmic antigens are not fully deleted, these cells are prime candidates for being the cells responsible for the breakdown of self-tolerance. The repetitive structure of SLE autoantigens crosslink immunoglobulin receptors on nondeleted, self-reactive B cells. For example, B cells can bind DNA, which then endocytose the DNA–DNA-binding protein complex. B cells then process this complex and present the relevant peptides to T cells. This reaction normally would result in T-cell anergy, because resting B cells cannot provide the required costimulatory signals that are needed for activation. Activated B cells, however, can deliver this costimulatory signal and trigger certain T cells to become fully responsive to self-antigens. Alternatively, activated T cells can induce resting B cells to become responsive. This is the case in GVH disease, where activated donor CD4+ cells can provide this second signal to permit B-cell activation and trigger autoantibody production (446, 447) (Table 10.8). Either of these situations therefore permits the development of expanded clones of autoreactive T cells and memory B cells that are capable of making specific autoantibodies. As stated, once memory cells have been generated, the opportunity for further autoantibody production is substantially increased.

The genes encoding many IgM anti-IgG and low-affin-

Table 10.7. Initiation of Systemic Lupus Erythematosus

1. Genetic predisposition ↓	Major histocompatibility complex class II susceptibility alleles (for autoantibodies)
	Deletion of genes encoding serum complement components
	Female sex hormones.
2. Inciting factors(s) ↓	Regulation of cytotoxic T cell activity
	Infectious agents, sunlight, drugs, or other environmental trigger factors
3. Persistant immune response ↓	Failure to eliminate inciting agent (virus or bacteria)
	Chronic inflammation with loss of regulatory CD8+ T cell activity
	Increased lymphocyte apoptosis resulting in increased challange of nuclear autoantigens
	Increased polyclonal B cells activity
4. Breakdown of tolerance (nonresponsiveness)	Reversal of clonal anergy and activation of self-reactive autoaggressive T cells because of defective suppressor cell activity
	Pathogenic autoantibodies and immune complexes. Onset of clinical disease

ity, cross-reactive nuclear autoantibodies are transcribed directly from germline and are highly conserved in phylogeny. It has been proposed that the role of B cells with surface IgM anti-IgG may be to capture immune complexes bearing infectious agents, thus serving as antigen-presenting cells for T cells (448). These autoantigen-specific B cells do not generally produce autoantibodies. In normal individuals who are exposed to intense immunologic stimulation, these cells may transiently produce IgM autoantibodies. In individuals who develop SLE, however, T-cell help induces a switch to IgG-autoantibody-producing cells.

Impaired Function of CD8+ and Other Regulatory T Cells

The developmental defects of CD8+ T-cell regulatory and effector cell activities undoubtedly are critical factors in the pathogenesis of SLE. The lupus-like syndrome resulting from chronic GVH disease in mice is a particularly illustrative example of the importance of CD8+ T cells (410) and is supported by older studies of murine chronic GVH reactions as well (446, 447, 449, 450). In addition, besides their cytotoxic activities, the regulatory properties of CD8+ T cells also are aberrant in human SLE. These cells inhibit IL-2 production and provide B-cell help (128, 139). Until recently, the sequence of events leading to the generation of T cells that downregulate antibody production were poorly understood. Studies from our laboratory, however, have suggested that TGF-β is a critical cofactor for the generation of these cells, and that an interaction between activated NK cells and CD8+ cells provides the active form of TGF-β for CD8+ cells to develop suppressor effector activity (decribed later). Therefore, the finding that patients with SLE have a defect in their ability to convert the latent complex of TGF-β to its active form may be important.

Without functional suppressor cells, the adjuvant afters of microbial infections might permit naive autoreactive anergic on "ignorant" (see above) T cells to undergo clonal expansion and become memory T cells. In fact, T cells that provide specific help for anti-DNA antibody production in SLE display the memory phenotype (21). Because memory cells have a low threshold for activation, subsequent exposure to nucleoprotein antigens along with the appropriate costimulatory factors can precipitate the onset of autoimmune disease.

Through a combination of genetic and environmental factors, therefore, there is a loss of tolerance to certain nuclear and cytoplasmic antigens, and specific T cells emerge that have the ability to provide B-cell help for a panoply of autoantibodies. Although the initial self-antigen that is recognized may be very specific, the phenomenon of epitope spreading with presentation of cryptic peptides by B cells broadens the original response. Recruitment of other nontolerant self-reactive T cells broadens the response even further and leads to generalized autoimmunity. Ultimately, B cells produce IgG autoantibodies that are often complement-fixing. At the onset of disease, therefore, antigen-stimulated T cells which produce IFNγ may be activated to provide the help required for these IgG antibodies. In established human SLE and some mouse models, T cells producing IFNγ are downregulated, however, as a consequence of chronic immune stimulation. Other mechanisms are involved in the perpetuation of SLE.

Table 10.8. Generalized Autoimmunity in SLE

1. IgG autoantibodies which are directed against self-antigens structures that can cross-link B cell Ig receptors.
2. These self antigens include: cell surface molecules such as CD4 or CD45; intracellular molecules with a repetitive structure, such as DNA; and highly charged molecules with a repetitive structure, such as the phospholipid target of the lupus anticoagulant.
3. In normals, binding of these self-antigens to B cell receptors induce nonresponsiveness.
4. In SLE, activated CD4+ T cells bind to resting self-reactive B cells and provide the co-stimulatory signals that trigger autoantibody formation. Alternatively, activated B cells function as fully competent antigen-presenting cells and induce resting autoreactive T cells to become specific helpers for autoantibody production.
5. Microbial superantigens are likely agents that bring CD4+ T cells and B cells into close contact and induce T cell activation.
6. In the absence of functional regulatory cells, autoantibodies will be produced.

T Cells in the Perpetuation of SLE

Increased Antigen Load

It has long been known that concentrations of DNA are increased in the serum of patients with SLE (452–454). Nucleosomes probably are the source of this DNA. Evidence has been reviewed earlier indicating increased numbers of activated T cells in patients with SLE. Activated cells are more susceptible than resting cells to the induction of apoptosis (455, 456). Lymphocytes isolated from patients with SLE undergo spontaneous apoptosis in culture at a faster rate than lymphocytes from normal or rheumatoid arthritis control subjects do. This accelerated in vitro apoptosis correlates with disease activity (457), suggesting that in fact, the in vivo–activated cells undergo accelerated in vitro apoptosis. Such activation-initiated increased apoptosis (assuming that the in vitro observations faithfully reflect the in vivo events) might be a source of nucleosomal material to sustain ongoing pathogenic autoantibody responses (457).

Increased circulating DNA in SLE not only can be explained by increased lymphocyte apoptosis but by de-

creased clearance of this material as well. Nucleosomes normally are quickly removed by phagocytic cells and by C-reactive protein (CRP), which binds chromatin, snRNPs, some histones, and membrane phospholipids. Phagocytic defects and decreased levels of CRP are well established in SLE (188, 458–460). Treatment of NZB/NZW F1 mice with CRP decreases autoantibody formation and increases survival (461).

Altered Cytokine Homeostasis

One consequence of active SLE, and the consequence of chronic inflammation, is elevated IL-10 production (199, 200). This is a homeostatic response to downregulate macrophages and lymphocytes that are activated by persistent immunologic stimulation. Among the cytokines that are downregulated by IL-10 are IL-2, TNF-α, and IFN-γ (99, 100). Each of these cytokines have been considered to have an important role in the generation of lymphocytes that downregulate antibody production. Moreover, recent studies performed in our laboratory have revealed that IL-10 inhibits the production of both latent and active TGF-β (86). As reviewed earlier, there is strong evidence that TNF-α has a protective effect in lupus mice and in the development of lupus nephritis in humans, but the mode of action for this cytokine is has remained elusive. We have documented that TNF-α can enable lymphocytes to convert latent TGF-β to its active form (86), which could be important in SLE as these individuals' lymphocytes have a defective capacity to perform this activity. One attractive possibility therefore is that the protective role of TNF-α may stem from its ability to upregulate the generation of regulatory cells.

Table 10.9. Perpetuation of SLE

1. Immune responses by clonally expanded T and B memory cells are directed against self antigens in which tolerance has been broken.
2. Because of T cell dysfunction, CD8+ T cells and NK cells provide help for B cells instead of down-regulating antibody production.
3. Other down-regulatory circuits are defective (mononuclear phagocyte system, idiotype networks, etc.).

Restoring Normal Homeostasis

Once SLE is induced, it must be sustained by one or more clones of autoreactive memory T cells that can respond to self-peptides that are derived from nuclear structures (Table 10.9). As indicated earlier, such autoreactive T-cell clones normally are downregulated through suppressor mechanisms, but such mechanisms are dysfunctional in active SLE (20, 462). A simplified model of the pathologic immune circuit in SLE is shown in Figure 10.1 and is based on recent studies performed in our laboratory (discussed earlier). In healthy individuals, CD4+ cells, facilitated by the generation of active TGF-β, induce CD8+ T-suppressor cells. Among several possible sources, this cytokine is produced following an interaction between activated CD8+ cells and NK cells. In SLE, however, CD8+ and NK cells support, instead of suppress, B-cell function. In our view, this is a consequence of inadequate help being provided by CD4+ cells (i.e., insufficient IL-2) and poor cross-talk between CD8+ cells and NK cells that results in the failure to generate active TGF-β. Lack of this cytokine may be critical in the dysfunctional activities of CD8+ cells.

Disruption of the interaction between activated CD4+ cells and autoantibody-producing B cells is a potential strategy to consider in the treatment of SLE. The interaction between CD40 expressed by B cells and CD40L expressed by activated T cells is a critical signal for B-cell differentiation, as discussed earlier (58, 59). A brief treatment of lupus mice with a monoclonal antibody against CD40 ligand greatly decreased the onset of lupus nephritis (463).

One would predict that the interruption of pathologic circuits and restoration of normal immune function would correlate with disease remission. In fact, remissions with reconstitution of T-cell function have been observed in patients who are treated with oral cyclophosphamide. In these patients, clinical improvement, disappearance of anti-DNA antibodies, normalization of complement, and

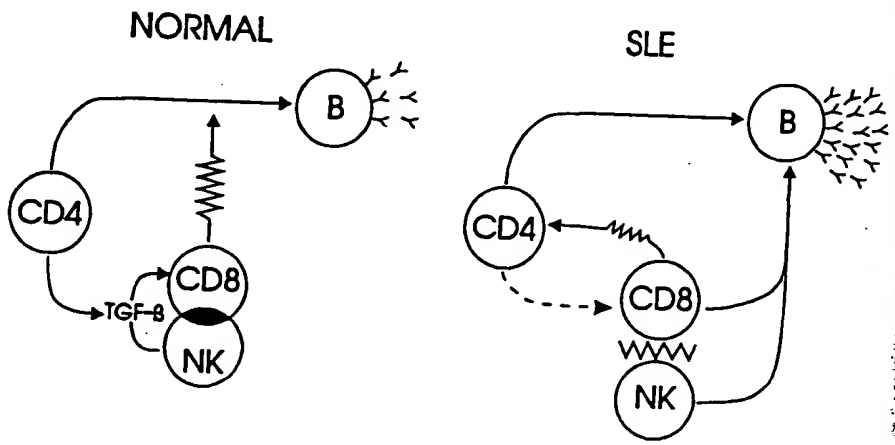

FIGURE 10.1. Regulation of antibody production in normal subjects and in patients with SLE. In healthy individuals, antigen-stimulated CD4+ T lymphocytes provide help for antibody production. CD4+ T cells also are involved in the generation of regulatory CD8+ cells, but by themselves, they cannot perform this function. TGF-β provided by NK or other cells is an important costimulatory factor for this function (109). In SLE, CD8+ cells inhibit IL-2 production. The "cross-talk" between CD8+ cells and the cells which provide TGF-β does not occur. Jagged arrows indicate suppressor activity.

disappearance of the sequelae of chronic inflammation were followed by the normalization of T-cell proliferation in SLE (464). One case was described in which clinical remission correlated with the normalization of IL-2 production, normalization of serum IL-2-receptor levels, and increase in CD8+ DR+ memory cells (465). In mice, antagonism of IL-10 has delayed the onset of SLE by upregulating TNF-α (201). A similar strategy is possible in human SLE. Based on the current, rapid progress in clarifying circuits that are involved in both normal and pathologic immune regulation, innovative strategies to manage SLE can be developed that allow normal homeostatic mechanisms to be re-established.

NK CELLS

NK cells have the ability to lyse particular tumor target cells in the absence of any obvious activating stimulus (466–468) and can kill certain cells that are infected by intracellular organisms (469). In addition to their cytotoxic properties, NK cells can enhance or suppress antibody production (470–472). After the features of NK cells are described in this section, their cytotoxic activities and regulatory effects in SLE are reviewed. Then, current views to explain why NK cells contribute to the suppression of antibody production in healthy subjects, but have the opposite effect in patients with SLE, are discussed.

Features of NK Cells

It now is evident that NK cells comprise a lymphocyte population that clearly is distinct from T and B cells. NK cells originally were identified by their ability to lyse a certain panel of tumor target cells in short-term cytotoxicity assays (466–468). Because activated T cells also have cytotoxic activity and NK cells and T cells share certain common surface markers (e.g., CD2) (473, 474), it initially was suspected that NK cells represented a subpopulation of T cells. However, unlike T cells, they lack specific receptors that are capable of recognizing peptide antigens (475).

The monoclonal antibodies to CD11b, CD16, and CD56 react predominantly with NK cells (476–479). CD11b is a receptor for the complement component C3bi, called the *complement type 3 receptor* or *CR3* (480). This molecule also is a member of the integrin or LeuCAM family of adhesion molecules and is expressed on approximately 15 to 20% of peripheral blood lymphocytes (481, 482). CD16 is a low-affinity receptor for IgG, termed *type III Fc receptor (FcR)*, and is expressed on approximately 10 to 15% of peripheral blood lymphocytes (483). CD56 is a neural cell adhesion molecule (NCAM) and is expressed on approximately 15 to 20% of peripheral blood lymphocytes (484). All CD16+ lymphocytes are CD11b+ and CD56+; that is, CD16+ lymphocytes are a subpopulation of CD11b+ and CD56+ lymphocytes (478, 485). Both CD11b and CD56 identify virtually identical lymphocyte populations (486).

Table 10.10. Charact ristics of NK Cells

Definition:
Natural killer (NK) cells are a population of lymphocytes distinct from T and B cells which spontaneously lyse tumor target cells.
Phenotype:
CD3−, Lack T-cell receptors (TCR/CD3 complex)
CD2+, >50% of NK cells express receptors for sheep red blood cells
CD11b+, Type 3 complement receptors
CD16+, Type 3 Fc receptors for IgG
CD56+, Neural cell adhesion molecule
Normal values:
10–15% of blood lymphocytes
Decreased percentages in active SLE
Cytotoxicity:
Endogenous decreased in active SLE
IL-2 stimulated: normal or decreased in active SLE
IFNγ stimulated: decreased in active SLE
Antibody-dependent cellular cytotoxicity (ADCC): decreased in active SLE

There is a small percentage of CD11b+ or CD56+ lymphocytes that coexpress the T-cell marker, CD3 (478, 487); however, the most highly cytolytic population is CD3- (478, 487). It is the CD11b+CD3- or CD56+CD3- lymphocytes that are NK cells, and these cells represent a distinct, third population of lymphocytes in addition to T and B lymphocytes (488).

Another important feature that distinguishes NK cells from T and B cells is their ability to respond directly to IL-2 and IFN-γ (489, 490). Resting T and B cells generally require a first signal to respond to these cytokines. Surface markers that characterize NK cells are reviewed in Table 10.10.

Numbers of NK Cells in SLE

Both the percentage and the absolute numbers of NK cells generally are decreased in patients with active SLE. The percentages of CD16+ cells are decreased (491–494), and the percentages of CD3-CD11b+ lymphocytes also are decreased (485). In patients with inactive SLE, values for NK cells usually are normal.

Cytotoxic Activity in SLE

In comparison to normal donors, patients with SLE have decreased NK cytotoxic activity; the decrease tends to be more pronounced in more active patients (495–500). Several explanations have been proposed to explain this abnormality, and these explanations are not necessarily mutually exclusive. Decreased NK activity may be explained by decreased percentages of NK cells. As stated earlier, CD16+ cells often are decreased in active SLE (491–494). This finding, however, may reflect modulation of CD16 from the cell surface by immune complexes rather than

decreased numbers of this subset. FcRs on the cell surface are modulated following exposure to immune complexes, and this results in a loss of cytotoxic activity (496, 500, 501). Supporting modulation of CD16 rather than a decrease in the number of NK cells is the finding that the numbers of lymphocytes binding NK-sensitive targets are comparable between normal donors and patients with SLE (497). Nonetheless, cytotoxic activity was decreased, which is a finding that suggests a defect in the actual lytic event in SLE (497). Therefore, NK cells in patients with active SLE may be defective in their capacity to lyse target cells.

Alternatively, "serum factors" also can account for decreased cytotoxic activity in SLE. One such serum factor is immune complexes, which are elevated in patients with active disease (502). When added to normal donor PBMCs, immune complexes suppress or decrease NK cytotoxic activity (496, 500, 501). However, most studies with SLE PBMC implied (rather than actually demonstrated) that immune complexes in the serum decreased the NK cytotoxic activity.

ALAs in SLE serum also have been considered as a cause of decreased NK activity. Several groups have reported that incubation with serum from patients with SLE followed by treatment with complement greatly decreased NK cytotoxic activity (495, 498, 499). The inability of serum alone to decrease NK activity suggests that immune complexes were not involved; whether the ALAs are specific for NK cells is unknown. One study demonstrated that serum from patients with SLE plus complement did kill a substantial number of NK cells (499). In this study, preincubation of the serum with T lymphocytes removed the cytotoxic activity, suggesting that the antibodies were not NK cell specific. However, another study described the presence of autoantibodies that were specific for CD16 (503). As stated elsewhere in this volume, there are ALAs in SLE that react with a variety of cell surface structures, some of which may have the potential to react with NK cells specifically or to prevent mediation of full functional activity.

As most NK cells express FcRs, these cells also are capable of mediating antibody-dependent cellular cytotoxicity (ADCC). This activity also is decreased in SLE (504–507), which is a finding that would be expected because of decreased expression of CD16 by NK cells in SLE.

SLE sera can contain IgG ALAs that are capable of sensitizing cells for ADCC. One report demonstrated that sera from patients with active SLE can induce ADCC activity against peripheral blood lymphocytes (508). This finding provides a mechanism that could explain, at least in part, the observed lymphopenia in SLE.

Certain cytokines such as IL-2 or IFN can augment NK cytotoxic activity (489, 490, 509–512). One group reported that NK cell activity can be restored to normal levels by IL-2, whereas IFN is more variable and usually less effective (145). Another group, however, was unable to correct the defect with either IL-2 or IFN-γ (513). Although the ability of SLE PBMCs to produce IL-2 in vitro in response to mitogenic stimulation is impaired (116, 514), whether there is a relationship between IL-2 production and NK cytotoxic activity is not known.

NK cells have the ability to kill almost all tumor target cells after a brief culture with IL-2 (515–517). This is called *lymphokine-activated killer cell (LAK) activity*. Only two studies on the generation of LAK cell activity in patients with SLE have been reported, and these are contradictory. One describes decreased LAK cell generation, and the other describes normal levels (141, 518). Clearly, there simply is a paucity of data to make any conclusions regarding the status of LAK cell generation in SLE.

NK Cell Suppressor Activity

Early studies on B-cell regulation by NK cells demonstrated that NK cells could suppress antibody production. By far, most of these studies measured the effect of NK cells on antibody production in pokeweed mitogen cultures, although similar results were obtained when Epstein-Barr virus–transformed B cells were used as a source of antibody-producing cells (470, 471, 519–520). A further reduction in the amount of antibody produced resulted if the NK cells were pretreated with IFN-α or IL-2 (470, 471). Some studies reported that suppressive activity was augmented by stimulating the NK cells with immune complexes (521). As NK cells express one class of receptor for the Fc portion of Ig (FcR III), it was suggested that stimulation through this receptor could induce suppressor activity. This would have been an attractive possibility regarding SLE, because elevated levels of immune complexes are associated with the disease. However, not all investigators have found that immune complexes stimulate or enhance suppressor activity (470, 519). Moreover, this mechanism clearly is absent or impaired in SLE, because a major problem in this disease is the lack of antibody suppression.

The finding that IFN-α and IL-2 enhance suppressive as well as cytotoxic activity suggested cytolysis as a possible mechanism of suppression. However, most studies have concluded that this is not a likely mechanism. In cultures where purified NK cells were added to purified B cells in the presence of T cell–derived supernatants, no suppression of antibody was found (519). In fact, the addition of NK cells enhanced antibody production in these cultures. Suppression only became evident when T cells were included in the cultures, and this suggested that suppression of antibody production by NK cells is mediated indirectly by T cells. Using pokeweed mitogen–stimulated cultures, Katz et al. (522) also demonstrated that NK cell–associated suppression was dependent on the presence of T cells.

Although NK cells have cytolytic capability, studies of B-cell viability as determined by measuring apoptotic activity or by susceptibility to cytolysis have excluded this as a mechanism of suppression (523, 524). Rather, the NK cells appear to support the generation of suppressor activity. On activation, CD8+ T cells can promote the production of both latent and active TGF-β from NK cells (525). Once in its active form, TGF-β can mediate a variety of

functions, including tissue repair and inflammation (526). Regarding immune cell function, TGF-β tends to be associated with inhibitory activity (527). However, TGF-β also can support some immune cell functions, and in particular, the addition of TGF-β to activated CD8+ T cells resulted in the generation of suppressor cells (525). It might be expected that if the functional activity of either the NK or the CD8+ T cell is aberrant, then suppression of antibody production might be affected. Of interest, both NK and CD8+ cell function are aberrant in SLE.

The significance of the NK cells' role in the suppression of antibody production has been demonstrated in several murine models of SLE. With certain strain combinations, the injection of parental spleen cells into F1 hybrid mice can result in the development of a lupus-like disease with autoantibody production. An inverse correlation was found between the levels of anti-dsDNA antibody and both the number and function of NK cells (528). The significance of this observation was shown by the reduction of autoimmunity through procedures that elevate NK activity and the exacerbation of symptoms by depleting the animals of NK cells. Similarly, it has been reported that development of autoimmunity in C56BL/6 lpr mice correlated with the disappearance of NK cells (529). In a more recent study of C57BL/6 lpr mice, the onset of autoimmunity correlated with the disappearance of a distinct population of cells that expressed the phenotype of NK cells but that also expressed TCRs (451). Taken together, these studies suggest that NK cells have an important role in the regulation of antibody production in vivo.

NK Cell Helper Activity

The first report that NK cells may stimulate rather than suppress the activity of B cells was that of Vyakarnam et al. (472). These authors demonstrated that when added to a B cell–enriched population, NK cell clones induced the production of antibodies. Subsequently, Kimata et al. (530) reported that freshly isolated, human peripheral blood NK cells could enhance the production of antibody by various B-lymphoblastoid-cell lines. Moreover, as mentioned earlier, it was found in studies trying to determine the mechanism of suppression that in the absence of T cells, NK cells enhanced rather than suppressed antibody production (519, 521).

Studies of patients receiving bone marrow transplants also have suggested that NK cells can support antibody production in vivo (531). Recipients of T cell–depleted allogeneic bone marrow can synthesize high titers of antibody. While they have few detectable T cells, these patients do have normal levels of NK cells that appear to be activated and can induce autologous B cells to produce antibody in vitro. That B-cell hyperactivity in SLE similarly may be supported, at least in part, by NK cells is indicated by studies from our laboratory in which full restoration of antibody production by purified B cells required the presence NK as well as T cells (130). Thus, the regulatory effects of NK cells in SLE are not related to the cytotoxic activities. Consistent with this are the studies of Procopio et al. (532), which demonstrated that NK clones could mediate helper activity in the absence of cytotoxic activity.

Several investigators have described B-cell factors in the supernatants of NK cells or their clones (472, 532, 533, 535). These factors include supernatants that support B-cell growth and/or B-cell differentiation. Of the supernatants that support B-cell differentiation, two have been characterized, at least to some degree. Becker et al. (533), using NK clones and B cells activated by stimulation with *Staphylococcus aureus* Cowan (SAC) and IL-2, reported that neutralizing antibodies to TNF-α inhibited the enhancement of antibody production. Moreover, activated, but not resting, B cells stimulated TNF-α production from the NK clones. Also using SAC- and IL-2–stimulated B cells, Jelinek and Lipsky (534) reported that TNF-α could augment antibody production. The TNF-α enhancement was found to be late acting and effective only after initial B-cell activation. Kimata et al. (535) also described a late-acting B-cell differentiation factor produced by purified NK cells. Although the factor was not identified, TNF-α did not have activity in their system.

For B cells to differentiate, an additional signal to that provided by cytokines usually is required (536). NK cells recently have been shown to be capable of providing both signals to induce B-cell differentiation (180). In this study, unstimulated NK cells were able to provide the first signal, which required physical contact with the B cell. The second signal then was provided by supernatants from IL-2-activated NK cells. While the nature of the first signal in these experiments was identified as an interaction between CD11a (LFA-1) and CD54 (ICAM-1), the factor in the supernatants was elusive. In this manner, NK cells were able to stimulte resting B cells to differentiate, whereas in many of the preceding studies, NK-cell helper activity was demonstrated on already-activated B cells.

Summary

The ability of NK cells to either suppress or support antibody production at first seems paradoxic. However, virtually all of the studies on B-cell regulation are consistent with the following mode of action. In the absence of T cells, any regulatory effect of NK cells on B cells is one of help, whether it is support of B-cell growth or of differentiation. In the presence of functional CD8+ T cells, however, NK cells enhance the suppressive effects of these T cells. Thus, the direct helper effect of NK cells is to enhance antibody production, while the suppressive effect is indirect.

In determining the lymphocyte population(s) supporting antibody production in SLE, we have found T cell–depleted lymphocytes still produce antibody, although purified B cells did not. Moreover, the addition of SLE NK cells to B cells enhanced antibody production (130). These observations suggest that NK cells are involved in sustaining antibody production in SLE. Studies from our laboratory demonstrate that CD8+ cells in patients with active

Table 10.11. Regulatory Properties of NK C lls on Antibody Production

Direct:
NK cells can directly help B cells differentiate into antibody-forming cells. This direct effect is probably important in sustaining B-cell hyperactivity in SLE.
Indirect:
NK cells can enhance the suppressor activity of CD8+ T cells resulting in down-regulation of antibody production. Because of dysregulation of CD8+ cells in SLE patients with active disease, the suppressive effect of NK cells is decreased or absent.

SLE are dysfunctional and act as helper cells rather than suppressor cells (130). Thus, it is not surprising that NK cells enhance rather than suppress antibody production in SLE.

The effects of NK cells on B cells are reviewed in Table 10.11.

References

1. Glass D, Schur PH. Autoimmunity and systemic lupus erythematosus. In: Talal N, ed. Autoimmunity: genetic, immunologic, virologic and clinical aspects. New York: Academic Press, 1977:532–560.
2. Blaese RM, Grayson J, Steinberg AD. Elevated immunoglobulin secreting cells in the blood of patients with active systemic lupus erythematosus: correlation of laboratory and clinical assessment of disease activity. Am J Med 1980; 69:345–350.
3. Steinberg AD, Raveche ES, Laskin CA, Smith HR, Santoro T, Miller ML, Plotz PH. Systemic lupus erythematosus: insights from animal models. Ann Intern Med 1984;100:714–727.
4. Talal N. Autoimmunity and the immunologic network. Arthritis Rheum 1978;21:853–867.
5. Theofilopoulos AN, Dixon FJ. Murine models of SLE. Adv Immunol 1985;37:269–285.
6. Horwitz DA. Impaired delayed hypersensitivity in systemic lupus erythematosus. Arthritis Rheum 1972;15:353–359.
7. Hahn BH, Bagby MK, Osterland CK. Abnormalities of delayed hypersensitivity in systemic lupus erythematosus. Am J Med 1973;55:25–31.
8. Paty JG Jr, Sienknecht CW, Townes AS, Hanissian AS, Miller JB, Masi AT. Impaired cell-mediated immunity in systemic lupus erythematosus (SLE). A controlled study of 23 untreated patients. Am J Med 1975;59:769–779.
9. Wofsy D, Seaman WE. Reversal of advanced murine lupus in NZB/NZW F1 mice by treatment with monoclonal antibody to L3T4. J Immunol 1987;138:3247–3253.
10. Mihara M, Ohsugi Y, Saito K, Miyai T, Togashi M, Ono S, Muakami S, Dobashi K, Hirayama F, Hamaoka T. Immunologic abnormality in NZB/NZW F1 mice. Thymus-independent occurrence of B cell abnormality and requirement for T cells in the development of autoimmune disease, as evidenced by an analysis of the athymic nude individuals. J Immunol 1988;141:85–90.
11. Shoenfeld Y, Mozes E. Pathogenic idiotypes in autoimmunity: lessons from new experimental models of SLE. FASEB J 1990;4:2646–2651.
12. Molina JF, Citera G, Rosler D, Cuellar ML, Molina J, Felipe O, Espinoza LR. Coexistence of human immunodeficiency virus infection and systemic lupus erythematosus. J Rheumatol 1995;22:347–345.
13. Burkly LC, Lo D, Flavell RA. Tolerance in transgenic mice expressing major histocompatibility molecules extrathymically on pancreatic cells. Science 1990;248:1364–1368.
14. Goodnow CC, Adelstein S, Basten A. The need for central and peripheral tolerance in the B cell repertoire. Science 1990;248:1373–1379.
15. Budman DR, Merchant EB, Steinberg AD, Doft B, Gershwin ME, Lizzio E, Reeves JP. Increased spontaneous activity of antibody-forming cells in the peripheral blood of patients with active SLE. Arthritis Rheum 1977;20:829–833.
16. Ginsburg WW, Finkelman FD, Lipsky PE. Circulating and pokeweed mitogen-induced immunoglobulin-secreting cells in systemic lupus erythematosus. Clin Exp Immunol 1979; 35:76–88.
17. O'Dell JR, Bizar-Scheebaum A, Kotzin BL. In vitro antihistone antibody production by peripheral blood cells from patients with SLE. Clin Immunol Immunopath 47:343–53, 1988.
18. Gharavi AE, Chu JL, Elkon KB. Autoantibodies to intracellular proteins in humans SLE are not due to random polyclonal B cell activation. Arthritis Rheum 1988;31:1337–1345.
19. Morris SC, Cheek RL, Cohen PL, Eisenberg RA. Autoantibodies in chronic graft versus host result from cognate T-B interactions. J Exp Med 1990;171:503–517.
20. Takeuchi T, Abe T, Koide J, Hosono O, Morimotos C, Homma M. Cellular mechanism of DNA-specific antibody synthesis by lymphocytes from systemic lupus erythematosus patients. Arthritis Rheum 1984;27:766–773.
21. Shivakumar S, Tsokos GC, Datta SK. T cell receptor alpha/beta expressing double negative(CD4-/CD8-) and CD4+ T helper cells in human augment the production of pathogenic anti-DNA autoantibodies associated with lupus nephritis. J Immunol 1989;143:103–112.
22. Chess L, MacDermott P, Schlossman SF. Immunologic functions of isolated human lymphocyte populations. J Immunol 1985;1113–1121.
23. Karpus WJ, Swanborg RH. CD4+ suppressor cells inhibit the function of effector cells of experimental autoimmune encephalomyelitis through a mechanism involving transforming growth factor-beta. J Immunol 1991;146:1163–1168.
24. Takahashi T, Gray JD, Horwitz DA. Human CD8+ lymphocytes stimulated in the absence of CD4+ cells enhance IgG production by antibody-secreting B cells. Clin Immunol Immunopathol 1991;58:352–365.
25. Blackman M, Kappler J, Marrack P. The role of the T cell receptor in positive and negative selection of developing T cells. Science 1990;248:1335–1341.
26. Rathmell JC, Goodnow CC. Effects of the lpr mutation in elimination and inactivation of self-reactive B cells. J Immunol 1994;153:2831–2842.
27. Freeman GJ, Borriello F, Hodes RJ, Reiser H, Gribben JG, Ng JW, Kim J, Goldberg JM, Hathcock K, Laszlo G, Lombard LA, Wang S, Gray GS, Nadler LM, Sharpe AH. Murine B7-2, an alternative CTLA4 counter-receptor that costimulates T cell proliferation and interleukin 2 production. J Exp Med 1993;178:2185–92.
28. Harding FA, Allison JP. CD28-B7 interactions allow the induction fo CD8+ cytotoxic T lymphocytes in the absence of exogenous help. J Exp Med 1993;177:1791–6.
29. Schwartz RH. A cell culture model for T lymphocyte clonal anergy. Science 1990;248:1349–1356.

30. Green DR, Scott DW. Activation-induced apoptosis in lymphocytes. Curr Opin Immunol 1994;6:476–487.
31. Norton SD, Hovinen DE, Jenkins MK. IL-2 secretion and T cell clonal anergy are induced by distinct biochemical pathways. J Immunol 1991;146:1125–1129.
32. Kanof ME, Strober W, Kwan WC, O'Connell NA, James SP. CD4+ Leu-8+ T cell supernatant activity that inhibits Ig production. J Immunol 1991;147:155–161.
33. McKeever U, Mordes JP, Greiner DL, Appel MC, Rozing J, Handler ES, Rossini AA. Adoptive transfer of autoimmune diabetes and thyroiditis to thymic rats. Proc Natl Acad Sci U S A 1990;87:7618–7622.
34. Taurog JD, Sandberg GP, Mahowald ML. The cellular basis of adjuvant arthritis. I. Enhancement of cell-mediated passive transfer by concanavalin A and by immunosuppressive treatment of the recipient. Cell Immunol 1983;75:271–82.
35. Ohashi PS, Oehen S, Buerki K, Pircher H, Ohashi CT, Odermatt B, Malissen B, Zinkernage RM, Hengartner H. Ablation of "tolerance" and induction of diabetes by vrius infection in viral antigen transgenic mice. Cell 1991;65:305–317.
36. Ehlers S, Smith KA. Differentiation of T cell lymphokine gene expression: the in vitro acquisition of T cell memory. J Exp Med 1991;173:25–36.
37. Akbar AN, Terry L, Timms A, Beverley PCL, Janossy G. Loss of CD45R and gain of UCHL1 is a feature of primed T cells. J Immunol 1988;140:2171–2178.
38. Beverley P. Immunological memory in T cells. Curr Opin Immunol 1991;3:355–360.
39. Byrne JA, Butler JL, Cooper MD. Differential activation requirements for virgin and memory T cells. J Immunol 1988; 141:3249–3257.
40. Clement LT, Yamashita N, Martin AM. The functionally distinct subpopulations of human CD4+ helper/inducer T lymphocytes defined by anti-CD45R antibodies derive sequentially from a differentiation pathway that is regulated by activation-dependent post-thymic differentiation. J Immunol 1988;141:1464–1470.
41. Merkenschlager M, Beverley PC. Evidence for differential expression of CD45 isoforms for memory dependent and independent cytotoxic responses: human CD8 memory CTL precursors selectively express CD45RO (UCHL1). Int Immunol 1989;1:450–457.
42. Yamashita N, Clement LT. Phenotypic characterization of the post-thymic differentiation of human alloantigen-specific CD8+ cytotoxic T lymphocytes. J Immunol 1989; 143:1518–1523.
43. Stewart SJ, Prpic V, Powers FS, Bocckino SB, Isaacks RE, Exton JH. Perturbation of the human T-cell antigen receptor-T3 complex leads to the production of inositol tetrakisphosphate: evidence for conversion from inositol trisphosphate. Proc Natl Acad Sci U S A 1986;83:6098–6102.
44. Nishizuka Y. The role of protein kinase C in cell surface signal transduction and tumour promotion. Nature 1984; 308:693–698.
45. Gardner P. Calcium and T lymphocyte activation. Cell 1989;59:15–20.
46. Bocckino SB, Blackmore PF, Wilson PB, Exton JH. Phosphatidate accumulation in hormone-treated hepatocytes via a phospholipase D mechanism. J Biol Chem 1987; 262:15309–15315.
47. Rosoff PM, Savage N, Dinarello CA. Interleukin-1 stimulates diacylglycerol production in T lymphocytes by a novel mechanism. Cell 1988;54:73–81.
48. Gelfand EW, Cheung RK, Mills GB, Grinstein S. Uptake of extracellular Ca^{2+} and not recruitment from internal stores is essential for T lymphocyte proliferation. Eur J Immunol 1988;18:917–922.
49. Weiss MJ, Daley JF, Hodgdon JC, Reinherz EL. Calcium dependency of antigen-specific (T3-Ti) and alternative (T11) pathways of human T-cell activation. Proc Natl Acad Sci U S A 1984;81:6836–6840.
50. Gelfand EW, Cheung RK, Grinstein S, Mills GB. Characterization of the role for calcium influx in mitogen-induced triggering of human T cells. Identification of calcium-dependent and calcium-independent signals. Eur J Immunol 1986; 16:907–912.
51. Gardner P, Alcover A, Kuno M, Moingeon P, Weyand CM, Goronzy J, Reinherz EL. Triggering of T-lymphocytes via either T3-Ti or T11 surface structures opens a voltage-insensitive plasma membrane calcium-permeable channel: requirement for interleukin-2 gene function. J Biol Chem 1989;264:1068–1076.
52. Truneh A, Albert F, Golstein P, Schmitt-Velhulst A-M. Early steps of lymphocyte activation bypassed by synergy between calcium ionophores and phorbol ester. Nature 1985; 313:318–320.
53. Nel AE, Bouic P, Lattanze GR, Stevenson HC, Miller P, Dirienzo W, Stefanini GF, Galbraith MR. Reaction of T lymphocytes with anti-T3 induces translocation of C-kinase activity to the membrane and specific substrate phosphorylation. J Immunol 1987;138:3519–3524.
54. Averill LE, Stein RL, Kammer GM. Control of human T-lymphocyte interleukin-2 production by a cAMP-dependent pathway. Cell Immunol 1988;115:88–99.
55. Damle NK, Linsley PS, Ledbetter JA. Direct helper T cell-induced B cell differentiation involves interaction between T cell antigen CD28 and B cell activation antigen B7. Eur J Immunol 1991;21:1277–1282.
56. Stohl W, Elliot JE, Linsley PS. Polyclonal in vitro T cell proliferation and differentiation supported by activated autologous B cells. Clin Immunol Immunopath 1994;72:44–72.
57. Gimmi CD, Freeman GJ, Gribben JG, Sugita K, Freedman AS, Morimoto C, Nadler LM. B-cell surface antigen B7 provides a costimulatory signal that induces T cells to proliferate and secrete interleukin 2. Proc Natl Acad Sci U S A 1991;88:6575–6579.
58. Lederman S, Yellin MJ, Krichevsky A, Belko J, Lee JJ, Chess L. Identification of a novel surface protein on activated $CD4^+$ T cells that induces contact-dependent B cell differentiation (help). J Exp Med 1992;175:1091–1101.
59. Noelle RJ, Roy M, Shepherd DM, Stamenkovic I, Ledbetter JA, Aruffo A. A 39-kDa protein on activated helper T cells binds CD40 and transduces the signal for cognate activation of B cells. Proc Natl Acad Sci U S A 1992;89:6550–6554.
60. Holder MJ, Wang H, Milner AE, Casamayor M, Armitage R, Spriggs MK, Fanslow WC, MacLennan ICM, Gregory CD, Gordon J. Suppression of apoptosis in normal and neoplastic human B lymphocytes by CD40 ligand is independent of Bcl-2 induction. Eur J Immunol 1993;23:2368–2371.
61. Tsubata T, Wu J, Honjo T. B-cell apoptosis induced by antigen receptor crosslinking is blocked by a T-cell signal through CD40. Nature 1993;364:645–648.
62. Lederman S, Yellin MJ, Cleary AM, Pernis A, Inghirami G, Cohn LE, Covey LR, Lee JJ, Rothman P, Chess L. T-BAM/CD40-L on helper T lymphocytes augments lymphokine-induced B cell Ig isotype switch recombination and rescues B cells from programmed cell death. J Immunol 1994; 152:2163–2171.
63. Garrone P, Neidhardt E-M, Garcia E, Galibert L, van Kooten C, Banchereau J. Fas ligation induces apoptosis of

CD40-activated human B lymphocytes. J Exp Med 1995; 182:1265–1273.
64. Schattner EJ, Elkon KB, Yoo D-H, Tumang J, Krammer PH, Crow MK, Friedman SM. CD40 ligation induces Apo-1/Fas expression on human B lymphocytes and facilitates apoptosis through the Apo-1/Fas pathway. J Exp Med 1995; 182:1557–1565.
65. Yellin MJ, Sippel K, Inghirami G, Covey LR, Lee JJ, Sinning J, Clark EA, Chess L, Lederman S. CD40 molecules induce down-modulation and endocytosis of T cell surface T cell-B cell activating molecule/CD40-L: potential role in regulating helper effector function. J Immunol 1994;152:598–608.
66. Ranheim EA, Kipps TJ. Activated T cells induce expression of B7/BB1 on normal or leukemic B cells through a CD40-dependent signal. J Exp Med 1993;177:925–935.
67. Suda T, Takahashi T, Golstein P, Nagata S. Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. Cell 1993;75:1169–1178.
68. Ramsdell F, Seaman MS, Miller RE, Picha KS, Kennedy MK, Lynch DH. Differential ability of T_h1 and T_h2 T cells to express Fas ligand and to undergo activation-induced cell death. Int Immunol 1994;6:1545–1553.
69. Stalder T, Hahn S, Erb P. Fas antigen is the major target molecule for $CD4^+$ T cell-mediated cytotoxicity. J Immunol 1994;152:1127–1133.
70. Hanabuchi S, Koyanagi M, Kawasaki A, Shinohara N, Matsuzawa A, Nishimura Y, Kobayashi Y, Yonehara S, Yagita H, Okumura K. Fas and its ligand in a general mechanism of T-cell-mediated cytotoxicity. Proc Natl Acad Sci U S A 1994;91:4930–4934.
71. Vignaux F, Golstein P. Fas-based lymphocyte-mediated cytotoxicity against syngeneic activated lymphocytes: a regulatory pathway? Eur J Immunol 1994;24:923–927.
72. Alderson MR, Tough TW, Davis-Smith T, Braddy S, Falk B, Schooley KA, Goodwin RG, Smith CA, Ramsdell F, Lynch DH. Fas ligand mediates activation-induced cell death in human T lymphocytes. J Exp Med 1995;181:71–77.
73. Brunner T, Mogil RJ, LaFace D, Yoo NJ, Mahboubi A, Echeverri F, Martin SJ, Force WR, Lynch DH, Ware CF, Green DR. Cell-autonomous Fas (CD95)/Fas-ligand interaction mediates activation-induced apoptosis in T-cell hybridomas. Nature 1995;373:441–444.
74. Dhein J, Walczak H, Bäumier C, Debatin K-M, Krammer PH. Autocrine T-cell suicide mediated by APO-1/(Fas/CD95). Nature 1995;373:438–441.
75. Ju S-T, Panka DJ, Cui H, Ettinger R, El-Khatib M, Sherr DH, Stanger BZ, Marshak-Rothstein A. Fas(CD95)/FasL interactions required for programmed cell death after T-cell activation. Nature 1995;373:444–448.
76. Rothstein TL, Wang JKM, Panka DJ, Foote LC, Wang Z, Stanger B, Cui H, Ju S-T, Marshak-Rothstein A. Protection against Fas-dependent Th1-mediated apoptosis by antigen receptor engagement in B cells. Nature 1995;374:163–165.
77. Kayagaki N, Kawasaki A, Ebota T, Ohmoto H, Ikeda S, Inoue S, Yoshino K, Okumura K, Yagita H. Metalloproteinase-mediated release of human Fas Ligand. J Exp Med 1995;182:1777–1783.
78. Owens T. A role for adhesion molecules in contact-dependent T help for B cells. Eur J Immunol 1991;21:979–983.
79. Fernandez-Botran R, Sanders VM, Mossman TR, Vitetta ES. Lymphokine-mediated regulation of the proliferative response of T helper 1 and T helper 2 cells. J Exp Med 1988; 168:543–558.
80. Romagnani S. Lymphokine production by human T cells in disease states. Annu Rev Immunol 1994;12:227–258.
81. Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance antigen-specific adaptive immunity. Annu Rev Immunol 1995;13:251–76.
82. Moore KW, O'Garra A, de Waal Malefyt R, Vieira P, Mosmann, TR. Interleukin-10. Annu Rev Immunol 1993; 11:165–90.
83. Kelker HC, Oppenheim J, Stone-Wolff DS, Henriksen-DeStefano D, Aggarwa BB, Stevenson HC, Vilcek J. Independent regulation of tumernecrosis factor and lymphotoxin production b, human peripheral blood lymphocytes. Int J Cancer 1985;36:69–73.
84. Cuturi MC, Murphy M, Costa-Giomi MP, Weinmann R, Perussia B, Trincieri G. Characterization of human tumor necrosis factor produced by peripheral blood monocytes and its separation from lymphotoxin. J Exp Med 1987; 165:1581–1594.
85. Roberts AB, Sporn MB. Transforming growth factor. Adv Cancer Res 1988;51:107–145.
85a. Gray JD, Hirokawa M, Ohtsuka K, Stimmler MM, Horwitz DA. Contrasting effects of anti-CD2 and anti-CD3 monoclonal antibodies in triggering an inhibitory circuit dependent on TGFβ provided by NK cells. Submitted for publication.
86. Fox FE, Ford HC, Douglas R, Cherian S, Nowell PC. Evidence that T6F-B can inhibit human T-lymphacyte proliferation through paracrine and autocrine mechanisms. Cell Immunol. 1993;150:45–48.
87. Callard RE, Smith SH, Scott KE. The role of interleukin 4 in specific antibody responses by human B cells. Int Immunol 1991;3:157–163.
88. Becker S, Daniel EG. Antagonistic and additive effects of IL-4 and interferon-gamma on human monocytes and macrophages: effects on Fc receptors, HLA-D antigens, and superoxide production. Cell Immunol 1990;129:351–362.
89. Standiford TJ, Strieter RM, Chensue SW, Westwick J, Kasahara K, Kunkel SL. IL-4 inhibits the expression of IL-8 from stimulated human monocytes. J Immunol 1990; 145:1435–1439.
90. Van Snick J. Interleukin 6: an overview. Annu Rev Immunol 1990;8:253–278.
91. Geppert TD, Davis LS, Gur H, Wacholtz MC, Lipsky PE. Accessory cell signals involved in T-cell activation. Immunol Rev 1990;117:5–66.
92. Heslop HE, Gottlieb DJ, Bianchi ACM, Meager A, Prentice HG, Mehta AB, Hoffbrand AV, Brenner MK. In vivo induction of gamma interferon and tumor necrosis factor by interleukin-2 infusion following intensive chemotherapy or autologous marrow transplantation. Blood 1989;74:1374–1380.
93. Kasid A, Director EP, Rosenberg SA. Induction of endogenous cytokine-MRNA in circulating peripheral blood mononuclear cells by IL-2 administration to cancer patients. J Immunol 1989;143:736–739.
94. Dinarello CA. Interleukin-1 and its biologically related cytokines. Adv Immunol 1989;44:153–205.
95. Holsti MA, Raulet DH. IL-6 and IL-1 synergize to stimulate IL-2 production and proliferation of peripheral T cells. Center for Cancer Research, Massachusetts Institute of Technology, Cambridge. J Immunol 1989;143:2514–2519.
96. Renauld JC, Vink A, Van Snick J. Accessory signals in murine cytolytic T cell responses. Dual requirement for IL-1 and IL-6. J Immunol 1989;143:1894–1898.
97. Shiba K, Stohl W, Gray JD, Horwitz DA. A novel role for

accessory cells in T cell-dependent B cell differentiation. Cell Immunol 1990;127:458–469.
98. Mosmann TR. Properties and functions of interleukin-10. Adv Immunol 1994;56:1–26.
99. de Waal Malefyt R, Yssel H, De Vries JE. Direct effect of IL-10 on subsets of human CD4+ T cell clones and resting T cells. Specific inhibition of IL-2 production and proliferation. J Immunol 1993;150:4754–4765.
100. Ding L, Shevach EM. IL-10 inhibits mitogen-induced T cell proliferation by selectively inhibiting macrophage costimulatory function. J Immunol 1992;148:3133–3139.
101. Wilder R. Neuroendocrine-immune system interactions and autoimmunity. Annu Rev Immunol 1995;13:307–338.
102. Fast LD. Generation and characterization of IL-2 activated veto cells. J Immunol 1992;149:1510–1515.
103. Powell TJ Jr, Streilein JW. Neonatal tolerance induction by class II alloantigens activates IL-4-secreting, tolerogen-responsive T cells. J Immunol 1990;144:854–859.
104. Schurmans S, Heusser CH, Qin HY, Merino J, Brighouse G, Lambert PH. In vivo effects of anti-IL-4 monoclonal antibody on neonatal induction of tolerance and on an associated autoimmune syndrome. J Immunol 1990;145:2465–2473.
105. Tada T, Ohzeki S, Utsumi K, Takiuchi H, Muramatsu M, Li XF, Shimizu J, Fujiwara H, Hamaoka T. Transforming growth factor-beta-induced inhibition of T cell function. Susceptibility difference in T cells of various phenotypes and functions and its relevance to immunosuppression in the tumor-bearing state. J Immunol 1991;146:1077–1082.
106. de Jong R, van Lier R, Ruscetti F, Schmitt C, Debre P, Mossalayi M. Differential effect of transforming growth factor-β1 on the activation of human naive and memory CD4+ T lymphocytes. Intern Immunol 1994;6:631–8.
107. Kehrl JH, Wakefield LM, Roberts AB, Anderson PM, Roberts AB, Jakowiew S, Alvarez-Mon M, Derynck R, Sporn MB, Fauci AS. Production of transforming growth factor β by human T lymphocytes and its potential role in the regulation of T cell growth. J Exp Med 1986;163:1037–50.
108. Wahl SM, Hunt DA, Wong HL, Dougherty S, McCartney-Francis N, Wahl LM, Ellingsworth L, Schmidt JA, Hall G, Roberts AB, Sporn MB. Transforming growth factor is potent immunosuppressive agent that inhibits IL-1 dependent lymphocyte proliferation. J Immunol 1988;140:3026–32.
109. Gray JD, Hirokawa M, Horwitz DA. The role of transforming growth factor beta in the generation of suppression: an interaction between CD8+ T cells and NK cells. J Exp Med 1994;180:1937–1942.
110. Luger TA, Smolen JS, Chused TM, Steinberg AD, Oppenheim JJ. Human lymphocytes with either OKT4 or OKT8 phenotype produce interleukin 2 in culture. J Clin Invest 1982;70:470–473.
111. Meuer SC, Hussey RE, Penta AC, Fitzgerald KA, Stadler BM, Schlossman SF, Reinherz EL. Cellular origin of interleukin 2 (IL 2) in man: evidence for stimulus-restricted IL 2 production by T4+ and T8+ T lymphocytes. J Immunol 1982;129:1076–1079.
112. Bender A, Kabelitz D. CD4-CD8- human T cells: phenotypic heterogeneity and activation requirements of freshly isolated "double negative" T cells. Cell Immunol 1988; 128:542–554.
113. Klinman DM, Steinberg AD. Inquiry into murine and human lupus. Immunol Rev 1995;144:157–193.
114. Sierakowski S, Kucharz EJ, Lightfoot RW, Goodwin JS. Impaired T-cell activation in patients with systemic lupus erythematosus. J Clin Immunol 1989;9:469–476.
115. Hishikawa T, Tokano Y, Sekigawa I, Ando S, Takasaki Y, Hashimoto H, Hirose S, Okumura K, Abe M, Shirai T. HLA-DP+T cells and deficient interleukin-2 production in patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1990;55:285–296.
116. Alcocer-Varela J, Alarcon-Segovia D. Decreased production of and response to interleukin-2 by cultured lymphocytes from patients with systemic lupus erythematosus. J Clin Invest 1982;69:1388–1392.
117. Linker-Israeli M, Bakke AC, Kitridou RC, Gendler S, Gillis S, Horwitz DA. Defective production of interleukin 1 and interleukin 2 in patients with systemic lupus erythematosus (SLE). J Immunol 1983;130:2651–2655.
118. Huang YP, Miescher PA, Zubler RH. The interleukin 2 secretion defect in vitro in systemic lupus erythematosus is reversible in rested cultured T cells. J Immunol 1986; 137:3515–3520.
119. Miyasaka N, Nakamura T, Russell IJ, Talal N. Interleukin-2 deficiencies in rheumatoid arthritis and systemic lupus erythematosus. Clin Immunol Immunopathol 1984;31: 109–117.
120. Murakawa Y, Sakane T. Deficient phytohemagglutinin-induced interleukin-2 activity in patients with inactive systemic lupus erythematosus is correctable by the addition of phorbol myristate acetate. Arthritis Rheum 1988;31:826–833.
121. Murakawa Y, Takada S, Ueda Y, Suzuki N, Hoshino T, Sakane T. Characterization of T lymphocyte subpopulations responsible for deficient interleukin 2 activity in patients with systemic lupus erythematosus. J Immunol 1985; 134:187–195.
122. Warrington RJ, Sauder PJ, Homik J, Ofosu-Appiah W. Reversible interleukin-2 response defects in systemic lupus erythematosus. Clin Exp Immunol 1989;77:163–167.
123. de Faucal P, Godard A, Peyrat MA, Moreau JF, Soulillou JP. Impaired IL-2 production by lymphocytes of patients with systemic lupus erythematosus. Ann Immunol 1984; 135:161–8.
124. Takada S, Ueda Y, Suzuki N, Murakawa Y, Hoshino Y, Green I, Steinberg AD, Horwitz PA, Sakane T. Abnormalities in autologous mixed lymphocyte reaction-activated immunologic processes in systemic lupus erythematosus and their possible correction by interleukin 2. Eur J Immunol 1985;15:262–267.
125. Via CS, Tsokos GC, Bermas B, Clerici M, Shearer GM. T cell-antigen presenting cell interactions in human systemic lupus erythematosus. Evidence for heterogeneous expression of multiple defects. J Immunol 1993;151:3914–22.
126. Sakane T, Murakawa Y, Nhoboru S, Ueda Y, Tsuchida T, Takada S, Yamauchi Y, Tsunematsu T. Familial occurrence of impaired interleukin-2 activity and increased peripheral blood B cells actively secreting immunoglobulins in systemic lupus erythematosus. Am J Med 1989;86:385–390.
127. Alcocer-Varela J, Alarcon-Segovia D. Longitudinal study on the production of and cellular response to interleukin-2 in patients with systemic lupus erythematosus. Rheumatol Int 1995;15:57–63.
128. Linker-Israeli M, Baake AC, Quismorio FP Jr, Horwitz DA. Correlation of interleukin-2 production in patients with systemic lupus erythematosus by removal of spontaneously activated suppressor cells. J Clin Invest 1985;75:762–768.
129. Linker-Israeli M, Gray JD, Quismorio FP Jr, Horwitz DA. Characterization of lymphocytes that suppress IL-2 production in systemic lupus erythematosus. Clin Exp Immunol 1988;73:236–241.
130. Linker-Israeli M, Quismorio FP Jr, Horwitz DA. Further characterization of interleukin-2 production by lympho-

cytes of patients with sytemic lupus erythematosus. J Rheumatol 1988;15:1216–1222.
131. Linker-Israeli M, Casteel N. Partial purification of systemic lupus erythematosus-derived factors that suppress production of interleukin-2. J Rheumatol 1988;15:952–958.
132. Sfikakis PP, Oglesby R, Sfikakis P, Tsokos GC. B7/BB1 provides an important costimulatory signal for CD3-mediated T lymphocyte proliferation in patients with systemic lupus erythematosus (SLE). Clin Exper Immunol 1994;96:8–14.
132a. Tsokos GC, Kovacs B, Sfikakis PP, Theocharis S, Vogelgesang S, Via CS. Defective antigen-presenting function in patients with systemic lupus erythematosus: role of the B7-1 (CD80) costinulatory molecule. Arthritis Rheum 1996; 39:600–609.
132b. Garcia-Cozer FJ, Molina IJ, Cuadrado MJ, Marubayashi M, Pena J. Sentamaria M. Defective B7 expression on antigen-presenting cells underlying T cell activation abnormalities in systemic lupus erythematosus (SLE) patients. Clin Exp Immunol 1996;104:72–79.
133. Miyagi J, Minato N, Sumiya M, Kasahara T, Kano S. Two types of antibodies inhibiting interleukin-2 production by normal lymphocytes in patients with systemic lupus erythematosus. Arthritis Rheum 1989;32:1356–1364.
134. Fukushima T, Kobayashi K, Kasama T, Kasahara K, Tabata M. Inhibition of interleukin-2 by serum in healthy individuals and in patients with autoimmune disease. Int Arch Allergy Appl Immunol 1987;84:135–141.
135. Kucharz EJ, Sierakowski S, Goodwin JS. Decreased activity of interleukin-2 inhibitor in plasma of patients with systemic lupus erythematosus. Clin Rheumatol 1988;7:87–90.
136. Huang YP, Perrin LH, Miescher PA, Zubler RH. Correlation of T and B cell activities in vitro and serum IL-2 levels in systemic lupus erythematosus. J Immunol 1988;141:827–833.
137. Warrington RJ. Interleukin-2 abnormalities in systemic lupus erythematosus and rheumatoid arthritis. A role for overproduction of interleukin-2 in human autoimmunity? J Rheumatol 1988;15:616–620.
138. Horwitz DA, Wang H, Gray JD. Cytokine gene profile in circulating blood mononuclear cells from patients with systemic lupus erythematosus: increased interleukin-2 but not interleukin 4 mRNA. Lupus 1994;3:423–428.
139. Linker-Israeli M, Quismorio FP, Jr, Horwitz DA. CD8+ lymphocytes from patients with systemic lupus erythematosus sustain rather than suppress spontaneous polyclonal IgG production and synergize with CD4+ cells to support autoantibody synthesis. Arthritis Rheum 1990;33:1216–1225.
140. Ishida H, Kumagai S, Unehara H, Sano H, Tagaya Y, Yodoi J, Imura H. Impaired expression of high affinity interleukin 2 receptor on activated lymphocytes from patients with systemic lupus erythematosus. J Immunol 1987;139:1070–1074.
141. Jira M, Strejcek J, Zavadil Z, Antosova E, Rejholec V. Interleukin-2 activated cells from peripheral blood of patients with systemic lupus erythematosus. Z Rheumatol 1990; 49:30–33.
142. Tanaka T, Saiki O, Negoro S, Igarashi T, Kuritani T, Hara H, Suemura M, Kishimoto S. Decreased expression of interleukin-2 binding molecules (p70/75) in T cells from patients with systemic lupus erythematosus. Arthritis Rheum 1989;32:552–559.
143. Saiki O, Tanaka T, Kishimoto S. Defective expression of p70/75 interleukin-2 receptor in T cells from patients with systemic lupus erythematosus: a possible defect in the process of increased intracellular calcium leading to p70/p75 expression. J Rheumatol 1990;17:1303–1307.
144. Takada S, Ueda Y, Suzuki N, Murakawa Y, Hosino T, Green L, Steinberg AD, Horwitz DA, Sakane T. Abnormalities in autologous mixed lymphocyte reaction-activated immunologic processes in systemic lupus erythematosus and their possible correction by interleukin 2. Eur J Immunol 1985;15:262–267.
145. Tsokos GC, Smith PL, Christian CB, Lipnick RN, Balow JE, Djeu JY. Interleukin-2 restores to depressed allogeneic cell-mediated lympholysis and natural killer cell activity in patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1985;34:379–386.
146. Volk HD, Diamantstein T. IL-2 normalizes defective suppressor T cell function of patients with systemic lupus erythematosus in vitro. Clin Exp Immunol 1986;66:525–31.
147. Wigfall DR, Sakai RS, Wallace DJ, Jordan SC. Interleukin-2 receptor expression in peripheral blood lymphocytes from systemic lupus erythematosus patients: relationship to clinical activity. Clin Immunol Immunopathol 1988;47:354–362.
148. Kishimoto T. Factors affecting B cell growth and differentiation. Annu Rev Immunol 1985;3:133–57.
149. Golbus J, Salata M, Greenwood J, Hudson J, Richardson BC. Increased immunoglobulin response to gamma-interferon by lymphocytes from patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1988;46: 129–140.
150. Blalock JE, Georgiades JA, Langford MP, Johnson HM. Purified human immune interferon has some potent anticellular activity than fibroblast or leukocyte interferon. Cell Immunol 1980;49:390–394.
151. Funauchi M, Sugishima H, Minoda M, Horiuchi A. Effect of interferon-gamma on B lymphocytes of patients with systemic lupus erythematosus. J Rheumatol 1991;18:368–372.
152. Braude IA, Hochberg MC, Arnett FC, Waldman TA. In vitro suppression of anti-DNA antibody and immunoglobulin synthesis in systemic lupus erythematosus patients by human gamma interferon. J Rheumatol 1988;15:438–444.
153. Schilling PJ, Kurzrock R, Kantarjian H, Gutterman JU, Talpaz M. Development of systemic lupus erythematosus after interferon therapy for chronic myelogenous leukemia. Cancer 1991;68:1536–1537.
154. Shiozawa S, Kuroki Y, Kim M, Hirohata S, Ogino T. Alpha-interferon in lupus psychosis (abstract). Arthritis Rheum 1991;34(Suppl):S51.
155. Machold KP, Smolen JS. Interferon-gamma induced exacerbation of systemic lupus erythematosus. J Rheumatol 1990;17:831–832.
156. Graninger WB, Hassfeld W, Pesau BB, Machold KP, Zielinski CC, Smolen JS. Induction of systemic lupus erythematosus by interferon-gamma in a patient with rheumatoid arthritis. J Rheum 1991;18:1621–1622.
157. Hirohata S, Miyamoto T. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. Arthritis Rheum 1990;33:644–649.
158. Hagiwara E, Gourley MF, Lee S, Klinman DM. Disease severity in patients with systemic lupus erythematosus correlates with an increased ration of IL-10: IFNγ-secreting cells in the peripheral blood. Arthritis Rheum 1996;39:379–85.
159. Tsokos GC, Rook AH, Djeu JY, Balow JE. Natural killer cells and interferon responses in patients with systemic lupus erythematosus. Clin Exp Immunol 1982;5:239–245.
160. Stolzenburg T, Binz H, Fontana A, Felder M, Wagenhaeuser FJ. Impaired mitogen-induced interferon-gamma production in rheumatoid arthritis and related diseases. Scand J Immunol 1988;27:73–81.
161. Tsokos GC, Boumpas DT, Smith PL, Djeu JY, Balow JE,

Rook AH. Deficient gamma-interferon production in patients with systemic lupus erythematosus. Arthritis Rheum 1986;29:1210–1215.
162. Rengaraju M, Gray JD, Horwitz DA, Kubin M, Trinchieri G. Increased spontaneous IL-10 production and decreased mitogen-induced IFNγ and TNFα production in untreated patients with SLE: role of CD8+ T cells. Lupus 1995; 4(Suppl 2):82.
163. Sibbitt WL Jr, Kenny C, Spellman CW, Ley KD, Bankhurst AD. Lympokines in autoimmunity: relationship between interleukin-2 and interferon-gamma production in systemic lupus erythematosus. Clin Immunol Immunopathol 1984; 32:166–173.
164. al-Janadi-M, al-Balla-S, al-Dalaan-A, Raziuddin-S. Cytokine profile in systemic lupus erythematosus, rheumatoid arthritis, and other rheumatic diseases. J Clin Immunol 1993;13:58–67.
165. Funauchi M, Sugishima H, Minoda M, Horiuchi A. Serum level of interferon-gamma in autoimmune diseases. Tohoku J Exp Med 1991;164:259–267.
166. Sibbitt WL Jr, Gibbs DL, Kenny C, Bankhurst AD, Searles RP, Ley KD. Relationship between circulating interferon and anti-interferon antibodies and impaired natural killer cell activity in systemic lupus erythematosus. Arthritis Rheum 1985;28:624–629.
167. Preble OT, Black RJ, Friedman RM, Klippel J, Vilcek J. Systemic lupus erythematosus: presence in human serum of the unusual acid labile leukocyte interferon. Science 1982; 216:429–431.
168. Kanayama Y, Kim T, Inariba H, Negoro N, Okamura M, Takeda T, Inoue T. Possible involvement of interferon alpha in the pathogenesis of fever in systemic lupus erythematosus. Ann Rheum Dis 1989;48:861–863.
169. Kim T, Kanayama Y, Okamura M, Takeda T, Inoue T. Serum levels of interferons in patients with systemic lupus erythematosus. Clin Exp Immunol 1987;70:562–569.
170. Matei I, Ghyka G, Savi I, Tudor A. Correlation of serum interferon with some clinical and humoral signs of systemic lupus erythematosus. Med Interne 1990;28:289–294.
171. Von Wussow P, Jakschies D, Hartung K, Deicher H. Presence of interferon and anti-interferon in patients with systemic lupus erythematosus. Rheum Int 1988;8:225–230.
172. Yee AM, Buyon JP, Yip YK. Interferon alpha associated with systemic lupus erythematosus is not intrinsically acid labile. J Exp Med 1989;169:987–993.
173. Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Annu Rev Immunol 1995;13:251–76.
174. Germann T, Bongartz M, Dlugonska H, Hess H, Schmitt E, Kolbe L, Kolsch E, Podlaski FJ, Gately MK, Rude E. Interleukin-12 profoundly up-regulates the synthesis of antigen-specific complement-fixing IgG2a, IgG2b and IgG3 antibody subclasses in vivo. Eur J Immunol 1995;25:823–9.
175. Jelinek DF, Braaten JK. Role of IL-12 in human B lymphocyte proliferation and differentiation. J Immunol 1995; 154:1606–1613.
176. Linker-Israeli M, Deans RJ, Wallace DJ, Prehn J, Ozeri-Chen T, Klinenberg JR. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. J Immunol 1991;147:117–123.
177. Dueymers M, Barrier J, Besancenot JF, Cledes J, Conri C, Dien G, Drosos AA, Dueymes JM, Galanaud P, Gribois B, Guillevin L, Hatron PY, Isenberg DA, Jorgensen C, Jouguan J, Lamour A, Le Faff P, Longy-Boursier M, Maron R, Massot C, Meyer O, Mottier D, Mountsopouios HM, Philippe P, Piette JC, Sany J, Series C, Shoenfeld Y, Youinou P. Relationship of interleukin-4 to isotypic distribution of anti-double-stranded DNA antibodies in sytemic lupus erythematosus. Int Arch Allergy Immunol 1993;101:408–416.
178. Parronchi P, Macchia D, Piccinni MP, Biswas P, Simonelli C, Maggi E, Ricci M, Ansari AA, Romagnani S. et al. Allergen- and bacterial antigen-specific T-cell established from atopic donors show a different profile of cytokine production. Proc Natl Acad Sci U S A 1991;88:4538–4542.
179. Scott P, Natovitz P, Coffman RL, Pearce E, Sher A. Immunoregulation of cutaneous leishmaniasis. T cell lines that transfer protective immunity or exacerbation belong to different T helper subset and respond to distinct parasite antigens. J Exp Med 1988;168:1675–1684.
180. Gray JD, Horwitz DA. Activated human natural killer cells can stimulate resting B lymphocytes cells to secrete immunoglobulin. J Immunol 1995;154:5656–5664.
181. Klashman DJ, Martin RA, Martinez-Maza O, Stevens RH. In vitro regulation of B cell differentiation by interleukin-6 and soluble CD23 in systemic lupus erythematosus B cell subpopulations and antigen-induced normal B cells. Arthritis Rheum 1991;34:276–286.
182. Hirose T, Hara M, Kitani A, Norioks K, Kawagoe M, Nakamura H. Abnormal production of and response to B-cell growth factor and B-cell differentiation factor in patients with systemic lupus erythematosus. Scand J Immunol 1985; 21:141–58.
183. Pelton BK, Denman AM. Spontaneous production of B cell growth factors by SLE lymphocytes. Clin Exp Immunol 1987;67:159–165.
184. Tanaka Y, Saito K, Shirakawa F, Ota T, Suzuki H, Eto S, Yamashita U. Production of B cell-stimulating factors by B cells in patients with systemic lupus erythematosus. J Immunol 1988;141:3043–3049.
185. Hashimoto C. Studies on synthesis of interleukin-6 and gammaglobulin in peripheral blood mononuclear cells of patients with systemic lupus erythematosus. Tohoku J Exp Med 1990;162:323–335.
186. al-Janadi-M. Raziuddin-S. B cell hyperactivity is a function of T cell derived cytokines in systemic lupus erythematosus. J Rheum 1993;20:1885–1891.
187. Spronk PE, Ter Borg EJ, Limburg PC, Kallenberg CGM. Plasma concentration of IL-6 in systemic lupus erythematosus: an indicator of disease activity? Clin Exp Immunol 1992;90:106–10.
188. Swaak AJG, van Rooyen A, Aarden LA. Interleukin-6 (IL-6) and acute phase proteins in the disease course of patients with systemic lupus erythematosus. Rheumatol Int 1989; 8:263–268.
189. Kroemer G, Martinez AC. Cytokines and autoimmune disease. Clin Immunol Immunopathol 1991;61:275–295.
190. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J Exp Med 1994;179:1317–1330.
191. Hefeneider SH, Brown LE, McCoy SL, Bakke AC, Cornell KA, Bennett RM. Immunization of BALB/c mice with a monoclonal anti-DNA antibody induces an anti-idiotypic antibody reactive with a cell-surface DNA binding protein. Autoimmunity 1993;15:187–194.
192. Pelton BK, Speckmaier M, Hylton W, Farrant J, Denman AM. Cytokine-independent progression of immunoglobulin production in vitro by B lymphocytes from patients with systemic lupus erythematosus. Clin Exp Immunol 1991; 83:274–279.
193. Kitani A, Hara M, Hirose T, Norioka K, Harigai M, Hirose W, Suzuki K, Kawakami M, Kawagoe M, Nakamura H. Heterogeneity of B cell responsiveness to interleukin 4, in-

terleukin 6 and low molecular weight B cell growth factor in discrete stages of B cell activation in patients with systemic lupus erythematosus. Clin Exp Immunol 1989;77:31–36.
194. Kitani A, Hara M, Hirose T, Harigai M, Suzuki K, Kawakami M, Kawaguchi Y, Hidaka T, Kawagoe M, Nakamura H. Autostimulatory effects of IL-6 on excessive B cell differentiation in patients with systemic lupus erythematosus: analysis of IL-6 production and IL-6R expression. Clin Exp Immunol 1992;88:75–83.
195. Nagafuchi H, Suzuki N, Mizushima Y, Sakane T. Constitutive expression of IL-6 receptors and their role in the excessive B cell function in patients with systemic lupus erythematosus. J Immunol 1993;151:6525–34.
196. Llorente L, Richaud-Patin Y, Fior R, Alcocer-Varela J, Wijdenes J, Fourrier BM, Galanaud P, Emilie D. In vivo production of interleukin-10 by non-T cells in rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus. A potential mechanism of B lymphocyte hyperactivity and autoimmunity. Arthritis Rheum 1994; 37:1647–1655.
197. Llorente L, Richaud-Patin Y, Wijdenes J, Alcocer-Varela J, Maillot MC, Durand-Gasselin I, Fourrier BM, Galanaud P, Emilie D. Spontaneous production of interleukin-10 by B lymphocytes and monocytes in systemic lupus erythematosus. Eur Cytokine Network 1993;4:421–427.
198. Houssiau FA, Lefebvre C, Vanden Berghe M, Lambert M, Devogelaer JP, Renauld JC. Serum interleukin 10 titers in systemic lupus erythematosus reflect disease activity. Lupus 1995;4:393–395.
199. Heinzel FP, Sadick MD, Mutha SS, Locksley RM. Production of interferon-gamma, Il-2, IL-4 and IL-10 by CD4+ lymphocytes in vivo during healing and progressive leishmaniasis. Proc Natl Acad Sci U S A 1991;59:4710–4714.
200. Clerici M, Wynn TA, Berzofsky JA, Blatt SP, Hendrix CW, Sher A, Coffman RL, Shearer GM. Role of interleukin-10 in T helper cell dysfunction in asymptomatic individuals infected with the human immunodeficiency virus. J Clin Invest 1994;93:768–775.
201. Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M. Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice. J Exp Med 1994;179:305–310.
202. Llorente L, Zou W, Levy Y, Richaud-Patin Y, Wijdenes J, Alcocer-Varela J, Morel-Fourrier B, Brouet JC, Alarcon-Segovia D, Galanaud P, Emile O. Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. J Exp Med 1995 181:839–844.
203. Aotsuka S, Nakamura K, Nakano T, Kawakami M, Goto M, Okawa-Takatsuji M, Kinoshita M, Yokohari R. Production of intracellular and extracellular interleukin-1 alpha and interleukin-1 beta by peripheral blood monocytes from patients with connective tissue diseases. Ann Rheum Dis 1991;50:27–31.
204. Hirose T. Spontaneous production of interleukin-1 and B cell stimulating factors by B cells from patients with systemic lupus erythematosus. Ryumachi 1989;29:277–283.
205. Jandl RC, George JL, Silberstein DS, Eaton RB, Schur PH. The effect of adherent cell-derived factors on immunoglobulin and anti-DNA synthesis in systemic lupus erythematosus. Clin Immunol Immunopathol 1987;42:344–359.
206. Sierakowski S, Kucharz EJ, Lightfoot RW Jr, Goodwin JS. Interleukin-1 production by monocytes from patients with systemic lupus erythematosus. Clin Rheum 1987;6:403–407.
207. Tanaka Y, Saito K, Suzuki H, Eto H, Yamashita U. Inhibitory effect of anti-class II antibody on the spontaneous activation of B cells in patients with systemic lupus erythematosus. Analysis with IL-1 production and IL-1 receptor expression. J Immunol 1989;143:1584–1590.
208. Cohen PL, Litvin DA, Winfield JB. Association between endogenously activated T cells and immunoglobulin-secreting B cells in patients with active systemic lupus erythematosus. Arthritis Rheum 1982;25:168–173.
209. Alcocer-Varela J, Laffon A, Alarcon-Segovia D. Defective monocyte production of, and T lymphocyte response to, interleukin-1 in the peripheral blood of patients with systemic lupus erythematosus. Clin Exp Immunol 1983;55:125–132.
210. Muzes G, Vien CV, Gonzalez-Cabello R, Feher J, Gergely P. Defective production of interleukin-1 and tumor necrosis factor alpha by stimulated monocytes from patients with systemic lupus erythematosus. Acta Medica Hungarica 1989;46:245–252.
211. Takei M, Kang H, Tomura K, Amaki S, Hirata M, Karasaki M, Sawsda S, Amaki I. Aberration of monokine production and monocyte subset in patients with systemic lupus erythematosus. J Clin Lab Immunol 1987;22:169–173.
212. Whicher JT, Gilbert AM, Westacott C, Hutton C, Dieppe PA. Defective production of leucocytic endogenous mediator (interleukin 1) by peripheral blood leucocytes of patients with systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and mixed connective tissue disease. Clin Exp Immunol 1986;65:80–89.
213. Horwitz DA, Linker-Israeli M, Gray JD. Lymphocyte and lymphokine abnormalities in patients with systemic lupus erythematosus. EOS J Immunol Immunopharm 1987;7:43–52.
214. Markenson JA, Lockshin MD, Fuzesi L, Warburg M, Joachim C, Morgan JW. Suppressor monocytes in patients with systemic lupus erythematosus. Evidence of suppressor activity associated with a cell-free soluble product of monocytes. J Lab Clin Med 1980;95:40–48.
215. Arend WP, Joslin FG, Massoni RJ. Effects of immune complexes on production by human monocytes of interleukin 1 or an interleukin 1 inhibitor. J Immunol 1985;134:3868–3875.
216. Gordon C, Wofsy D. Effects of recombinant murine tumor necrosis factor-α on immune function. J Immunol 1990; 144:1753–61.
217. Jacob CO, Fronek Z, Lewis GD, Koo M, Hansen JA, McDevitt HO. Heritable major histocompatibility complex class II-associated differences in production of tumor necrosis factor-α: relevance to genetic predisposition to systemic lupus erythematosus. Proc Natl Acad Sci U S A 1990; 87:1233–1237.
218. Mitamura K, Kang H, Tomita Y, Hashimoto H, Sawada S, Horie T. Impaired tumour necrosis factor-alpha (TNF-alpha) production and abnormal B cell response to TNF-alpha in patients with systemic lupus erythematosus (SLE). Clin Exp Immunol 1991;85:386–391.
219. Malave I, Searles RP, Montano J, Williams RC Jr. Production of tumor necrosis factor/cachectin by peripheral blood mononuclear cells in patients with systemic lupus erythematosus. Int Arch Allergy Appl Immunol 1989;89:355–361.
220. Maury CP, Teppo AM. Tumor necrosis factor in the serum of patients with systemic lupus erythematosus. Arthritis Rheum 1989;32:146–150.
221. Brennan DC, Yui MA, Wuthrich RP, Kelley VE Tumor necrosis factor and IL-1 in New Zealand black/white mice. J Immunol 1989;143:3470–3475.

222. Boswell JM, Yui MA, Burt DW, Kelley VE. Increased tumor necrosis factor and IL-1 beta gene expression in the kidneys of mice with lupus nephritis. J Immunol 1988;141:3050–3054.
223. Dang H, Geiser AG, Letterio JJ, Nakabayashi T, Kong L, Fernandes G, Talal N. SLE-like autoantibodies and Sjogren's syndrome-like lymphoproliferation in TGF-beta knockout mice. J Immunol 1995;155:3205–3212.
224. Yaswen L, Kulkarni AB, Fredrickson T, Mittleman B, Schiffmann R, Payne S, Longenecker G, Mozes E, Karlsson. Autoimmune manifestations in the transforming growth factor- 1 knockout mice. Blood 1996;87:1439–1445.
225. Raz E, Watanabe A, Baird SM, Eisenberg RA, Parr TB, Lotz M, Kipps TJ, Carson DA. Systemic immunological effects of cytokine genes injected into skeletal muscle. Proc Natl Acad Sci U S A 1993;90:4523–28.
226. Del Guidice G, Crow MK. Role of transforming growth factor beta in systemic autoimmunity. Lupus 1993;2:213–220.
227. Del Guidice G, Elkon KB, Crow MK. Evidence for TGFβ-mediated suppression of T cell proliferative response in patients with systemic lupus erythematosus (abstract). Arthritis Rheum 1991;34(Suppl):S137.
228. Glinski W, Gershwin ME, Steinberg AD. Fractionation of cells on a discontinuous Ficoll gradient. Study of subpopulations of human T cells using anti-T cell antibodies from patients with systemic lupus erythematosus. J Clin Invest 1976;57:604–614.
229. Horwitz DA, Juul-Nielsen K. Human blood L, lymphocytes in patients with active systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. Clin Exp Immunol 1977; 30:370–378.
230. Messner RP, Kindstrom FD, Williams JR Jr. Peripheral blood lymphocyte cell surface markers during the course of systemic lupus erythematosus. J Clin Invest 1973;52:3046–3056.
231. Moretta LM, Mingari MC, Webb SR, Pearl ER, Lydyard PM, Grossi CE, Lawton AR, Cooper MD. Imbalances in T cell subpopulations associated with immunodeficiency and autoimmune syndromes. Eur J Immunol 1984;7:696–700.
232. Rivero SJ, Diaz-Jouanen E, Alarcon-Segovia D. Lymphopenia in systemic lupus erythematosus. Arthritis Rheum 1978;21:295–305.
233. Rivero SJ, Llorente L, Diaz-Jouanen E, Alarcon-Segovia D. T-lymphocyte subpopulation in untreated systemic lupus erythematosus. Variations with disease activity. Arthritis Rheum 1977;20:1169–1173.
234. Morimoto C, Reinherz EL, Schlossman SF, Schur PH, Mills JA, Steinberg AD. Alteration in T cell subsets in active systemic lupus erythematosus. J Clin Invest 1980;66:1171–1174.
235. Tsokos GC, Balow JE. Phenotypes of T lymphocytes in systemic lupus erythematosus: decreased cytotoxic/suppressor subpopulation is associated with deficient allogenic cytotoxic responses rather than with concanavalin A-induced suppressor cells. Clin Immunol Immunopathol 1983; 26:267–276.
236. Smolen JS, Chused TM, Leiserson WM, Reeves JP, Alling D, Steinberg AD. Heterogeneity of immunoregulatory T-cell subsets in systemic lupus erythematosus. Am J Med 1982; 72:783–790.
237. Bakke AC, Kirkland PA, Kitridou RC, Quismorio FP, Rea T, Ehresmann GR, Horwitz DA. T lymphocyte subsets in systemic lupus erythematosus. Arthritis Rheum 1983; 26:745–750.
238. McInerney MF, Clough JD, Senitzer D, Cathcart MK. Two distinct subsets of patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1988;49:116–132.
239. Fornasieri A, Sinico R, Fiorini G, Goldaniga D, Colasanti G, Bendemia F, Gibelli A, D'Amic G. T-lymphocyte subsets in primary and secondary glomerulonephritis. Proc Eur Dial Transplant Assoc 1983;19:635–641.
240. Morimoto C, Reinherz EL, Distaso JA, Steinberg AD, Schlossman SF. Relationship between systemic lupus erythematosus T cell subsets, anti-T cell antibodies and T cell functions. J Clin Invest 1984;73;689–700.
241. Yamada A, Cohen PL, Winfield JB. Subset specificity of antilymphocyte antibodies in systemic lupus erythematosus. Preferential reactivity with cells bearing the T4 and autologous erythrocyte receptor phenotypes. Arthritis Rheum 1985;28:262–270.
242. Yamada A, Winfield JB. Inhibition of soluble antigen-induced T cell proliferation by warm-reactive antibodies to activated T cells in systemic lupus erythematosus. J Clin Invest 1984;74:1948–1960.
243. Butler WT, Sharp JT, Rossen RD, Lidsky MD, Mittal KK, Gard DA. Relationship of the clinical course of systemic lupus erythematosus to the presence of circulating lymphocytotoxic antibodies. Arthritis Rheum 1972;15:231–238.
244. DeHoratius RJ, Tunk KSK, Pincus T. Reduced T-lymphocyte subsets in systemic lupus erythematosus: effects of immune complexes and lymphocytotoxic antibodies. Clin Immunol Immunopathol 1980;17:235–256.
245. Messner RP, Kennedy MS, Kelinek JG. Antilymphocyte antibodies in systemic lupus erythematosus. Effect on lymphocyte surface characteristics. Arthritis Rheum 1975;18:201–206.
246. Ooi BS, Orlina AR, Pesce AJ, Mendoza N, Masaitis L, Pollak VE. Lymphocytotoxic antibodies in patients with systemic lupus erythematosus. Clin Exp Immunol 1974; 17:237–243.
247. Steinberg AD, Klassen LW, Budman DR, Williams GW. Immunofluorescence studies of anti-T cell antibodies and T cells in systemic lupus erythematosus. Arthritis Rheum 1979;22:114–122.
248. Winfield JB, Lobo PI, Singer A. Significance of anti-lymphocyte antibodies in systemic lupus erythematosus. Arthritis Rheum 1978;21(Suppl):S215–S221.
249. Winfield JB, Winchester RJ, Kunkel HG. Association of cold-reactive anti-lymphocyte antibodies with lymphopenia in systemic lupus erythematosus. Arthritis Rheum 1975; 18:587–594.
250. Alvarado C, Alcocer-Varela J, Llorente L, Richaud-Patin Y, Cerbon M, Alarcon-Segovia D. Effect of CD28 antibody on T cells from patients with systemic lupus erythematosus. J Autoimm 1994;7:763–73
251. Stohl W, Crow MK, Kunkel HG. Systemic lupus erythematosus with deficiency of the T4 epitope on T helper/inducer cells. N Engl J Med 1985;312:1671–1678.
252. Stohl W, Singer JZ. Correlation between systemic lupus erythematosus and T4 epitope phenotype. Arthritis Rheum 1987;30:1412–1415.
253. Brenner MB, McLean J, Dialynas DP, Strominger JL, Smith JA, Owen FL, Seidman JG, Ip S, Rosen F, Krangel MS. Identification of a putative second T-cell receptor. Nature 1986; 322:145–149.
254. Lanier LL, Testi R, Bindl J, Phillips JH. Identity of Leu19 (CD56) leucocyte differentiation antigen and neural cell adhesion molecule. J Exp Med 1990;169:2233–43.
255. Bell EB. Thymus-derived and non-thymus-derived T-like cells: the origin and function of cells bearing gamma delta receptors. Thymus 1989;14:3–17.

256. Rajagopalan S, Zordan T, Tsokos GC, Datta SK. Pathogenic anti-DNA autoantibody-inducing T helper cell lines from patients with active lupus nephritis. Isolation of CD4-8-T helper cell lines that express the gamma delta T-cell antigen receptor. Proc Natl Acad Sci U S A 1990;87:7020–7024.
257. Gerli R, Agea E, Bertotto A, Tognellini R, Flenghi L, Spinozzi F, Velardi A, Grignani F. Analysis of T cells bearing different isotypic forms of the gamma/delta T cell receptor in patients with systemic autoimmune diseases. J Rheumatol 1991;18:1504–10.
258. Morimoto C, Steinberg AD, Letvin NL, Hagan M, Takeuchi T, Daley J, Levine H, Schlossman SF. A defect of immunoregulatory T cell subsets in systemic lupus erythematosus patients demonstrated with anti-2H4 antibody. J Clin Invest 1987;79:762–768.
259. Raziuddin S, Nur MA, Al Wabel AA. Selective loss of the CD4+ inducers of suppressor T cell subsets (2H4+) in active systemic lupus erythematosus. J Rheumatol 1991; 16:1315–1319.
260. Sato K, Miyasaka N, Yamaoka K, Okuda M, Yata J, Nishioka K. Quantitative defect of CD4+2H4+ cells in systemic lupus. Arthritis Rheum 1987;30:1407–1411.
261. Mimura T, Fernsten P, Jarjour W, Winfield JB. Autoantibodies specific for different isoforms of CD45 in systemic lupus erythematosus. J Exp Med 1990;172:653–656.
262. Tanaka S, Matsuyama T, Steinberg AD, Schlossman SF, Morimoto C. Antilymphocyte antibodies against CD4+2H4+ cell populations in patients with systemic lupus erythematosus. Arthritis Rheum 1989;32:398–405.
263. Sanders ME, Magoda MW and Shaw S. Human naive and memory T cells: reinterpretation of helper-inducer and suppressor-inducer subsets. Immunol today 1988;9:195–199.
264. Dawisha SM, Gmelig-Meyling F, Steinberg AD. Assessment of clinical parameters associated with increased frequency of mutant T cells in patients with systemic lupus erythematosus. Arthritis Rheum 1994;37:270–277.
265. Theocharis S, Sfikakis PP, Lipnick RN, Klipple GL, Steinberg AD, Tsokos GC. Characterization of in vivo mutated T cell clones from patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1995;74:135–142.
266. Raziuddin S, Nur MA, Al Wabel AA. Increased circulating HLA-DR+ CD4+ T cells in systemic lupus erythematosus: alterations associated with prednisolone therapy. Scand J Immunol 1990;31:139–145.
267. Tsuchiya N, Mitamura T, Goto M, Moroi Y, Kinoshita M, Yokohari R, Miyamoto T. 2-Dimensional flow cytometric analysis of peripheral blood T lymphocytes from patients with systemic lupus erythematosus: preferential expression of HLA-DR antigen on the surface of Leu 2a+ cells. J Rheumatol 1988;15:946–951.
268. Inghirami G, Simon J, Balow JE, Tsokos GC. Activated T lymphocytes in the peripheral blood of patients with systemic lupus erythematosus induce B cells to produce immunoglobulin. Clin Exp Rheumatol 1988;6:269–276.
269. Murashima A, Takasaki Y, Ohgaki M, Hashimoto H, Shirai T, Hirose S. Activated peripheral blood mononuclear cells detected by murine monoclonal antibodies to proliferating cell nuclear antigen in active lupus patients. J Clin Immunol 1990;10:28–37.
270. Horwitz DA, Stastny P, Ziff M. Circulating deoxyribonucleic acid-synthesizing mononuclear leukocytes. I. Increased numbers of proliferating mononuclear leukocytes in inflammatory disease. J Lab Clin Med 1970;76:391–402.
271. Volk HD, Kopp J, Koerner IJ, Jahn S, Grunow R, Barthelmes H, Fiebig H. Correlation between the phenotype and the functional capacity of activated T cells in patients with active systemic lupus erythematosus. Scand J Rheumatol 1986;24:109–114.
272. Campen DH, Horwitz DA, Quismorio FP Jr, Ehresmann GR, Martin WJ. Serum levels of interleukin-2 receptor and activity of rheumatic disease characterized by immune system activation. Arthritis Rheum 1988;31:1358–1364.
273. Manoussakis MN, Papadopoulos GK, Drosos AA, Moutsopoulos HM. Soluble interleukin 2 receptor molecules in the serum of patients with autoimmune diseases. Clin Immunol Immunopathol 1989;50:321–332.
274. Deleted
275. ter Borg EJ, Horst G, Limburg PC, Kallenberg CGM. Changes in plasma levels of interleukin 2 receptor in relation to disease exacerbations and levels of anti-dsDNA and complement in systemic lupus erythematosus. Clin Exp Immunol 1990;82:21–26.
276. Wolf RE, Brelsford WG. Soluble interleukin-2 receptors in systemic lupus erythematosus. Arthritis Rheum 1988; 31:729–733.
277. Samsonov MY, Tilz GP, Egorova O, Reibnegger G, Balabanova RM, Nassonov EL, Nassonova VA, Wachter H, Fuchs D. Serum soluble markers of immune activation and disease activity in systemic lupus erythematosus. Lupus 1995;4:29–32.
278. Spronk PE, ter Borg EJ, Huitema MG, Limburg PC, Kallenberg CG. Changes in levels of soluble T-cell activation markers, sIL-2R, sCD4 and sCD8, in relation to disease exacerbations in patients with systemic lupus erythematosus: a prospective study. Ann Rheum Dis 1994;53:235–239.
279. Heilig B, Fiehn C, Brockhaus M, Gallati H, Pezzutto A, Hunstein W. Evaluation of soluble tumor necrosis factor (TNF) receptors and TNF receptor antibodies in patients with systemic lupus erythematosus, progressive systemic sclerosis, and mixed connective tissue disease. J Clin Immunol 1993;13:321–328.
280. Aderka D, Wysenbeek A, Engelmann H, Cope AP, Brennan F, Molad Y, Hornik V, Levo Y, Maini RN, Feldmann M, Wallach D. Correlation between serum levels of soluble tumor necrosis factor receptor and disease activity in systemic lupus erythematosus. Arthritis Rheum 1993;36:1111–1120.
281. Laskin CA, Smathers PA, Reeves JP, Steinberg AD. Studies of defective tolerance induction in NZB mice. Evidence for a marrow pre-T cell defect. J Exp Med 1982;155:1025–1036.
282. Gonzalez-Quintial R, Baccala R, Balderas RS, Theofilopoulos AN. V beta gene repertoire in the aging mouse: a developmental perspective. Int Rev Immunol 1995;12:27–40.
283. Scott DE, Kisch WJ, Steinberg AD. Studies of T cell deletion and T cell anergy following in vivo administration of SEB to normal and lupus-prone mice. J Immunol 1993;150:664–672.
284. Roark JH, Kuntz CL, Nguyen CA, Caton AJ, Erikson J. Breakdown of B cell tolerance in a mouse model of systemic lupus erythematosus. J Exp Med 1995;181:1157–1167.
285. Mixter PF, Russell JQ, Budd RC. Delayed kinetics of T lymphocyte anergy and deletion in lpr mice. J Autoimmun 1994;7:697–710.
286. Papiernik M, Pontoux C, Golstein P. Non-exclusive Fas control and age dependence of viral superantigen-induced clonal deletion in lupus-prone mice. Euro J Immunol 1995; 25:1517–1523.
287. Stohl W, Elliott JE, Hamilton AS, Deapen DM, Mack TM, Horwitz DA. Impaired recovery and cytolytic function of $CD56^+$ T and non-T cells in systemic lupus erythematosus

(SLE) following in vitro polyclonal T cell stimulation: studies in unselected SLE patients and in monozygotic twins discordant for SLE. Arthritis Rheum 1996; in press.
288. Kägi D, Vignaux F, Ledermann B, Bürki K, Depraetere V, Nagata S, Hengartner H, Golstein P. Fas and perforin pathways as major mechanisms of T cell-mediated cytotoxicity. Science 1994;265:528–530.
289. Lowin B, Hahne M, Mattmann C, Tschopp J. Cytolytic T-cell cytotoxicity is mediated through perforin and Fas lytic pathways. Nature 1994;370:650–652.
290. Walsh CM, Matloubian M, Liu C-C, Ueda R, Kurahara CG, Christensen JL, Huang MTF, Young JD-E, Ahmed R, Clark WR. Immune function in mice lacking the perforin gene. Proc Natl Acad Sci U S A 1994;91:10854–10858.
291. Kojima H, Shinohara N, Hanaoka S, Someya-Shirota Y, Takagaki Y, Katayama T, Yagita H, Okumura K, Shinkai Y, Alt FW, Matsuzawa A, Yonehara S, Takayama H. Two distinct pathways of specific killing revealed by perforin mutant cytotoxic T lymphocytes. Immunity 1994;1:357–364.
292. Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 1992;356:314–317.
293. Lynch DH, Watson ML, Alderson MR, Baum PR, Miller RE, Tough T, Gibson M, Davis-Smith T, Smith CA, Hunter K, Bhat D, Din W, Goodwin RG, Seldin MF. The mouse Fas-ligand gene is mutated in gld mice and is part of a TNF family gene cluster. Immunity 1994;1:131–136.
294. Takahashi T, Tanaka M, Brannan CI, Jenkins NA, Copeland NG, Suda T, Nagata S. Generalized lymphoproliferative disease in mice, caused by a point mutation in the Fas ligand. Cell 1994;76:969–976.
295. Ramsdell F, Seaman MS, Miller RE, Tough TW, Alderson MR, Lynch DH. gld/gld Mice are unable to express a functional ligand for Fas. Eur J Immunol 1994;24:928–933.
296. Cohen PL, Eisenberg RA. Lpr and gld: single gene models of systemic autoimmunity and lymphoproliferative disease. Annu Rev Immunol 1991;9:243–269.
297. Reap EA, Leslie D, Abrahams M, Eisenberg RA, Cohen PL. Apoptosis abnormalities of splenic lymphocytes in autoimmune lpr and gld mice. J Immunol 1995;154:936–943.
298. Wu J, Zhou T, Zhang J, He J, Gause WC, Mountz JD. Correction of accelerated autoimmune disease by early replacement of the mutated lpr gene with the normal Fas apoptosis gene in the T cells of transgenic MRL-lpr/lpr mice. Proc Natl Acad Sci U S A 1994;91:2344–2348.
299. Mysler E, Bini P, Drappa J, Ramos P, Friedman SM, Krammer PH, Elkon KB. The apoptosis-1/Fas protein in human systemic lupus erythematosus. J Clin Invest 1994;93:1029–1034.
300. Amasaki Y, Kobayashi S, Takeda T, Ogura N, Jodo S, Nakabayashi T, Tsutsumi A, Fujisaku A, Koike T. Up-regulated expression of Fas antigen (CD95) by peripheral naive and memory T cell subsets in patients with systemic lupus erythematosus (SLE): a possible mechanism for lymphopenia. Clin Exp Immunol 1995;99:245–250.
301. Ohsako S, Hara M, Harigai M, Fukasawa C, Kashiwazaki S. Expression and function of Fas antigen and bcl-2 in human systemic lupus erythematosus lymphocytes. Clin Immunol Immunopathol 1994;73:109–114.
302. Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IAG, Debatin KM, Fischer A, de Villartay JP. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science 1995;268:1347–1349.
303. Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 1995; 81:935–946.
304. Cheng J, Zhou T, Liu C, Shapiro JP, Brauer MJ, Kiefer MC, Barr PJ, Mountz JD. Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. Science 1994; 263:1759–1762.
305. Knipping E, Krammer PH, Onel KB, Lehman TJA, Mysler E, Elkon KB. Levels of soluble Fas/APO-1/CD95 in systemic lupus erythematosus and juvenile rheumatoid arthritis. Arthritis Rheum 1995;38:1735–1737.
306. Goel N, Ulrich DT, St. Clair EW, Fleming JA, Lynch DH, Seldin MF. Lack of correlation between serum soluble Fas/APO-1 levels and autoimmune disease. Arthritis Rheum 1995;38:1738–1743.
307. Vaux DL, Cory S, Adams JM. Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. Nature 1988;335:440–442.
308. Nunez G, Seto M, Seremetis S, Ferrero D, Grignani F, Korsmeyer SJ, Dalla-Favera R. Growth- and tumor-promoting effects of deregulated BCL2 in human B-lymphoblastoid cells. Proc Natl Acad Sci U S A 1989;86:4589–4593.
309. Tsujimoto Y. Overexpression of the human BCL-2 gene product results in growth enhancement of Epstein-Barr virus-immortalized B cells. Proc Natl Acad Sci U S A 1989; 86:1958–1962.
310. Strasser A, Whittingham S, Vaux DL, Bath ML, Adams JM, Cory S, Harris AW. Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. Proc Natl Acad Sci U S A 1991;88:8661–8665.
311. Gatenby PA, Irvine M. The bcl-2 proto-oncogene is overexpressed in systemic lupus erythematosus. J Autoimmun 1994;7:623–631.
312. Aringer M, Wintersberger W, Steiner CW, Kiener H, Presterl E, Jaeger U, Smolen JS, Graninger WB. High levels of bcl-2 protein in circulating T lymphocytes, but not B lymphocytes, of patients with systemic lupus erythematosus. Arthritis Rheum 1994;37:1423–1430.
313. Hashimoto S, Michalsky JP, Berman MA, McCombs C. Mechanism of a lymphocyte abnormality associates with HLA-B8/DR3: role of interleukin-1. Clin Exp Immunol 1990;79:227–232.
314. Alexander EL, McNicholl J, Watson RM, Bias W, Reichlin M, Provost TT. The immunogenetic relationship between anti-Ro(SS-A)/La(SS-B) antibody positive Sjogren's/lupus erythematosus overlap syndrome and the neonatal lupus syndrome. J Invest Dermatol 1989;93:751–756.
315. Arnett FC, Bias WB, Reveille JD. Genetic studies in Sjogren's syndrome and systemic lupus erythematosus. J Autoimmunity 1989;2:403–413.
316. Sasaki T, Shibata S, Hirabayashi Y, Sekiguchi Y, Yoshinaga K. Accessory cell activity of monocytes in anti-DNA antibody production in systemic lupus erythematosus. Clin Exp Immunol 1989;77:37–42.
317. Posnett DN, Gottlieb A, Bussel JB, Friedman SM, Chiorazzi N, Li Y, Szabo P, Farid NR, Robinson MA. T cell antigen receptors in autoimmunity. J Immunol 1988;141:1963–1969.
318. Wong DW, Bentwich Z, Martinez-Tarquino C, Seidman JG, Duby AD, Quertermous T, Schur PH. Nonlinkage of the T Cell Receptor α, β, and γ genes to systemic lupus erythematosus in multiplex families. Arthritis Rheum 1988; 31:1371–1376.
319. Tebib JG, Alcocer-Verela J, Alarcon-Segovia D, Schur PH. Association between a T cell receptor restriction fragment

length polymorphism and systemic lupus erythematosus. J Clin Invest 1990;86:1961–1967.
320. Naiki M, Chiang BL, Cawlely D, Ansari A, Rozzo SJ, Kotzin BL, Zlotnik A, Gershwin ME. Generation and characterization of clones T helper cell lines for anti-DNA responses in NZB.H-2m12 mice. J Immunol 1992;149:4109–4115.
321. Mohan C, Adams S, Stanik V, Datta SK. Nucleosome: a major immunogen for pathogenic autoantibody-inducing T cells of lupus. J Exp Med 1993;177:1367–1381.
322. Mao C, Osman GE, Adams S, Datta SK. T cell receptor alpha-chain repertoire of pathogenic autoantibody-inducing T cells in lupus mice. J Immunol 1994;152:1462–1470.
323. Desai-Mehta A, Mao C, Rajagopalan S, Robinson T, Datta SK. Structure and specificity of T cell receptors expressed by potentially pathogenic anti-DNA autoantibody-inducing T cells in human lupus. J Clin Invest 1995;95:531–541.
324. Hoffman RW, Takeda Y, Sharp GC, Lee DR, Hill DL, Kaneoka H, Caldwell CW. Human T cell clones reactive against U-small nuclear ribonucleoprotein autoantigens from connective tissue disease patients and health individuals. J Immunol 1993;151:6460–6469.
325. Crow MK, DelGiudice-Asch G, Zehetbauer JB, Lawson JL, Brot N, Weissbach H, Elkon KB. Autoantigen-specific T cell proliferation induced by the ribosomal P2 protein in patients with systemic lupus erythematosus. J Clin Invest 1994;94:345–352.
326. Singh RR, Kumar V, Ebling FM, Southwood S, Sette A, Sercarz EE, Hahn BH. T cell determinants from autoantibodies to DNA can upregulate autoimmunity in murine systemic lupus erythematosus. J Exp Med 1995;181:2017–2027.
327. Horwitz DA, Garrett MA. Lymphocyte reactivity to mitogens in subjects with systemic lupus erythematosus, rheumatoid arthritis and scleroderma. Clin Exp Immunol 1977; 27:92–99.
328. Lockshin ME, Eisenhauer AC, Kohn R, Weksler M, Block S, Mushlin DS. Cell-mediated immunity in rheumatic diseases. II. Mitogen responses in RA, SLE and other illnesses: correlation with T and B lymphocyte populations. Arthritis Rheum 1975;18:245–250.
329. Rosenthal CJ, Franklin EC. Depression of cellular-mediate mediated immunity in systemic lupus erythematosus. Relation to disease activity. Arthritis Rheum 1975;18:207–217.
330. Utsinger PD, Yount WJ. Phytohemagglutinin response to systemic lupus erythematosus. Reconstitution experiments using highly purified lymphocyte subpopulations and monocytes. J Clin Invest 1977;60:626–638.
331. Gottlieb AB, Lahita RG, Chiorazzi N, Kunkel HG. Immune function in systemic lupus erythematosus. Impairment of in vitro T-cell proliferation and in vivo antibody response to exogenous antigen. J Clin Invest 1979;63:885–892.
332. Kumagai S, Steinberg AD, Green I. Immune responses to hapten-modified self and their regulation in normal individuals and patients with systemic lupus erythematosus. J Immunol 1981;127:1643–1658.
333. Suciu-Foca N, Buda JA, Thiem T, Reemtsa K. Impaired responsiveness of lymphocytes in patients with systemic lupus erythematosus. Clin Exp Immunol 1974;18:295–302.
334. Tsokos GC, Balow JE. Cytotoxic responses to alloantigens in systemic lupus erythematosus. J Clin Immunol 1981; 1:208–211.
335. Kuntz MM, Innes JB, Weksler ME. The cellular basis of the impaired autologous mixed lymphocyte reaction in patients with systemic lupus erythematosus. J Clin Invest 1979; 63:151–153.
336. Sakane T, Steinberg AD, Arnett FC, Reinertsen JL, Green I. Studies of immune functions of patients with systemic lupus erythematosus. III. Characterization of lymphocyte subpopulations responsible for defective autologous mixed lymphocyte reactions. Arthritis Rheum 1979;22:770–776.
337. Sakane T, Steinberg AD, Green I. Failure of autologous mixed lymphocyte reactions between T and non-T cells in patients with systemic lupus erythematosus. Proc Natl Acad Sci U S A 1978;75:3464–3468.
338. Charpentier B, Carnoud C, Bach JF. Selective depression of the xenogeneic cell-mediated lympholysis in systemic lupus erythematosus. J Clin Invest 1979;64:351–360.
339. Stohl W. Impaired generation of polyclonal T cell-mediated cytolytic activity despite normal polyclonal T cell proliferation in systemic lupus erythematosus. Clin Immunol Immunopathol 1992;63:163–172.
340. Kammer GM. Impaired T cell capping and receptor regeneration in active systemic lupus erythematosus. Evidence for a disorder intrinsic to the T lymphocyte. J Clin Invest 1983; 72:1686–1697.
341. Kammer GM, Mitchell E. Impaired mobility of human T lymphocyte surface molecules during inactive systemic lupus erythematosus. Relationship to a defective CAMP pathway. Arthritis Rheum 1988;31:88–98.
342. Kammer G-M, Khan I-U, Malemud C-J. Deficient type I protein kinase A isozyme activity in systemic lupus erythematosus T lymphocytes. J Clin Invest 1994;94:422–430.
343. Deleted
344. Martorell J, Font J, Rojo I, Vilella R, Ingelmo M, Vives J. Responsiveness of systemic lupus erythematosus T cells to signals provided through LCA T200 (CD45) and T1 (CD5) antigens. Clin Exp Immunol 1989;78:172–176.
345. Stekman IL, Blasini AM, Leon-Ponte M, Baroja ML, Abadi I, Rodriguez MA. Enhanced CD3-mediated T lymphocyte proliferation in patients with systemic lupus erythematosus. Arthritis Rheum 1991;34:459–467.
346. Stohl W. Impaired polyclonal T cell cytolytic activity: a possible risk factor for systemic lupus erythematosus. Arthritis Rheum 1995;38:506–516.
347. Vassilopoulos D, Kovacs B, Tsokos GC. TCR/CD3 complex-mediated signal transduction pathway in T cells and T cell lines from patients with systemic lupus erythematosus. J Immunol 1995;155:2269–2281.
348. Tada Y, Nagasawa K, Yamauchi Y, Tsukamoto H, Niho Y. A defect in the protein kinase C system in T cells from patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1991;60:220–231.
349. Mandler R, Birch RE, Polmar SH, Kammer GM, Rudolph SA. Abnormal adenosine-induced immunosuppression and cAMP metabolism in T lymphocytes of patients with systemic lupus erythematosus. Proc Natl Acad Sci U S A 1982; 79:7542–7546.
350. Phi NC, Takáts A, Binh VH, Vien CV, González-Cabello R, Gergely P. Cyclic AMP level of lymphocytes in patients with systemic lupus erythematosus and its relation to disease activity. Immunol Lett 1989;23:61–64.
351. Hasler P, Schultz LA, Kammer GM. Defective cAMP-dependent phosphorylation of intact T lymphocytes in active systemic lupus erythematosus. Proc Natl Acad Sci U S A 1990;87:1978–1982.
352. Goldman JA, Litwin A, Adams LE, Krueger RC, Hess EV. Cellular immunity to nuclear antigens in systemic lupus erythematosus. J Clin Invest 1972;51:2669–2677.
353. Wernet P, Kunkel HG. Antibodies to a specific surface antigen on T cells in human sera inhibiting mixed leukocyte culture reactions. J Exp Med 1973;138:1021–1026.
354. Kuntz MM, Innes JB, Weksler ME. Lymphocyte transfor-

mation induced by autologous cells. IV. Human T-lymphocyte proliferation induced by autologous or allogeneic non-T lymphocytes. J Exp Med 1976;143:1042–1054.
355. Markenson JA, Lockshin MD, Fuzesi L, Warburg M, Joachim C, Morgan JW. Suppressor monocytes in patients with systemic lupus erythematosus. Evidence of suppressor activity associated with a cell-free soluble product of monocytes. J Lab Clin Med 1980;95:40–48.
356. Bell DA. Cell-mediated immunity in systemic lupus erythematosus: observations on in vitro cell-mediated immune responses in relationship to number of potentially reactive T cells, disease activity, and treatment. 1978;9:301–317.
357. Hamilton M, Normansell DE, Garrett MA, Davis JS 4th. Mitogen stimulation of human lymphocytes. II. Effect of exogenous DNA on lymphocyte function in systemic lupus erythematosus. Clin Immunol Immunopathol 1982; 22:238–246.
358. Malave I, Cuadra C. Impaired function of peripheral lymphocytes in systemic lupus erythematosus. Intern Arch Allergy Appl Immunol (N Y) 1977;55:412–419.
359. Patrucco R, Rothfield NF, Hirschhorn K. The response of cultured lymphocytes from patients with systemic lupus erythematosus to DNA. Arthritis Rheum 1967;10:32–37.
360. Sucia-Foca N, Buda JA, Thiem T, Reemtsa K. Impaired responsiveness of lymphocytes in patients with systemic lupus erythematosus. Clin Exp Immunol 1974;18:295–303.
361. Tsokos GC, Balow JE, Huston DP, Wei N, Decker JL. Effect of plasmapheresis on T and B lymphocyte functions in patients with systemic lupus erythematosus: a double blind study. Clin Exp Immunol 1982;48:449–457.
362. Horwitz DA. Mechanisms producing decreased mitogenic reactivity in patients with systemic lupus erythematosus and other rheumatic diseases in mitogens. In: Oppenheim JJ, Rosenstreich DL, eds. Mitogens and immunobiology. New York: Academic Press, 1976. Pp 625–638.
363. Horwitz DA, Cousar JB. A relationship between impaired cellular immunity, humoral suppression of lymphocytes function and severity of systemic lupus erythematosus. Am J Med 1975;58:829–835.
364. Horwitz DA, Garrett MA, Criag AH. Serum effects on mitogenic reactivity in subjects with systemic lupus erythematosus, rheumatoid arthritis and scleroderma. Clin Exp Immunol 1977;27:100–110.
365. Tovar Z, Dauphinee MJ, Talal N. Defective induction of T-cell help and natural killing following anti-CD3 stimulation of autoimmune lymphocytes. J Autoimmun 1988;1:327–337.
366. Stekman IL, Blasini AM, Leon-Ponte M, Baroja ML, Abadi I, Rodriguez MA. Enhanced CD3-mediated T lymphocyte proliferation in patients with systemic lupus erythematosus. Arthritis Rheum 1991;34:459–467.
367. Martorell J, Font J, Rojo I, Vilella R, Ingelmo M, Vives J. Responsiveness of systemic lupus erythematosus T cells to signals provided through LCA T200 (CD45) and T1 (CD5) antigens. Clin Exp Immunol 1989;78:172–176.
368. Fox D, Millard JA, Treisman J, Zeldes W, Bergman A, Depper J, Dunne R, McCune WJ. Defective CD2 pathway T cell activation in systemic lupus erythematosus. Arthritis Rheum 1991;34:561–571.
369. Horwitz DA, Tang FL, Oki A, Stimmler MM, Gray JD. A selective T cell defect in the response to anti-CD2 in systemic lupus erythematosus: reversal by anti-CD28 and monocyte depletion. Arthritis Rheum in press.
370. Bierer BE, Barbosa J, Herrmann S, Burakoff SJ. Interaction of CD2 with its ligand, LFA-3, in human T cell proliferation. J Immunol 1988;140:3358–3363.
371. Emilie D, Wallon C, Galanaud P, Fischer A, Olive D, Delfraissy J-F. Role of the LFA3-CD2 interaction in human specific B cell differentiation. J Immunol 1988;141:1912–1918.
372. Dohlsten M, Hedlund G, Lando PA, Trowsdale J, Altmann D, Patarroyo M, Fischer H, Kalland T. Role of the adhesion molecule ICAM-1 (CD54) in staphylococcal enterotoxin-mediated cytotoxicity. Eur J Immunol 1991;21:131–135.
373. Linsley PS, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med 1991;174:561–569.
374. Tohma S, Hirohata S, Lipsky PE. The role of CD11a/CD18-CD54 interactions in human T cell-dependent B cell activation. J Immunol 1991;146:492–499.
375. Tohma S, Lipsky PE. Analysis of the mechanisms of T cell-dependent polyclonal activation of human B cells: induction of human B cell responses by fixed activated T cells. J Immunol 1991;146:2544–2552.
376. Azuma M, Cayabyab M, Buck D, Phillips JH, Lanier LL. CD28 interaction with B7 costimulates primary allogeneic proliferative responses and cytotoxicity mediated by small, resting T lymphocytes. J Exp Med 1992;175:353–360.
377. Azuma M, Cayabyab M, Phillips JH, Lanier LL. Requirements for CD28-dependent T cell-mediated cytotoxicity. J Immunol 1993;150:2091–2101.
378. Stohl W, Elliott JE, Linsley PS. Human T cell-dependent B cell differentiation induced by Staphylococcal superantigens. J Immunol 1994;153:117–127.
379. Takeuchi T, Amano K, Sekine H, Koide J, Abe T. Upregulated expression and function of integrain adhesive receptors in systemic lupus erythmatosus patients with vasculitis. J Clin Invest 1993;92:3008–3016.
380. Richardson BC, Strahler JR, Pivirotto TS, Quddus J, Bayliss GE, Gross LA, O'Rourke KS, Powers D, Hanash SM, Johnson MA. Phenotypic and functional similarities between 5-azacytidine-treated T cells and a T cell subset in patients with active systemic lupus erythematosus. Arthritis Rheum 1992;35:647–662.
381. Sfikakis PP, Oglesby R, Sfikakis P, Tsokos GC. B7/BB1 provides an important costimulatory signal for CD3-mediated T lymphocyte proliferation in patients with systemic lupus erythematosus (SLE). Clin Exp Immunol 1994;96:8–14.
382. Tan P, Pang G, Wilson JD. Immunoglobulin production in vitro by peripheral blood lymphocytes in systemic lupus erythematosus: helper T cell defect and B cell hyperreactivity. Clin Exp Immunol 1981;44:548–554.
383. Fauci AS, Moutsopoulos HM. Polyclonally triggered B cells in the peripheral blood and bone marrow of normal individuals and in patients with systemic lupus erythematosus and Sjogren's syndrome. Arthritis Rheum 1981;24:577–583.
384. Nies KM, Stevens RH, Louie JS. Normal T cell regulation of IgG synthesis in systemic lupus erythematosus. J Clin Lab Immunol 1980;4:69–75.
385. Delfraissy JF, Second P, Galanaud P, Wallon C, Massias P, Dormont J. Depressed primary in vitro antibody response in untreated systemic lupus erythematosus. J Clin Invest 1980;11:141–142.
386. Kumagai S, Sredni B, House S, Steinberg AD, Green I. Defective regulation of B lymphocyte colony formation in patients with systemic lupus erythematosus. J Immunol 1982; 128:258–262.
387. Brodman R, Gilfillan, Glass D, Schur PH. Influenzal response in systemic lupus erythematosus. Ann Intern Med 1978;88:735–740.
388. Louie JS, Nies KM Shoji KT, Fraback RC, Abrass C, Border W, Cherry JD, Imagawa P. Clinical and antibody responses

after influenza immunization in systemic lupus erythematosus. Ann Intern Med 1978;88:790–792.
389. Shou L, Schwartz S, Good RA. Suppressor cell activity after concanavalin A treatment on lymphocytes from normal donors. J Exp Med 1978;143:1100–1110.
390. Abdou NI, Sagawa A, Passual E, Herbert G, Sadaghee S. Suppressor T cell abnormality in idiopathic systemic lupus erythematosus. Clin Immunol Immunopathol 1976;6:192–199.
391. Bresnihan B, Jasin HE. Suppressor function of peripheral blood mononuclear cells in normal individuals and in patients with systemic lupus erythematosus. J Clin Invest 1977;59:106–116.
392. Horowitz S, Borcherding H, Moothy AV, Chesny R, Schulte-Wisserman NH, Hong R, Goldstein A. Induction of suppressor T cells in systemic lupus erythematosus by thymosin and cultured thymic epithelium. Science 1977; 197:999–1001.
393. Morimoto C. Loss of suppressor T lymphocyte function in patients with systemic lupus erythematosus. Clin Exp Immunol 1978;32:125–133.
394. Sakane T, Steinberg AD, Green I. Studies of immune functions of patients with systemic lupus erythematosus. I. Dysfunction of suppressor T cell activity related to impaired generation of, rather than response to, suppressor cells. Arthritis Rheum 1978;21:657–664.
395. Falko JM, Williams JC, Harvey DG, Weidman SW, Schonfeld G, Dodson WE. Hyperlipoproteinemia and multifocal neurologic dysfunction in systemic lupus erythematosus. J Ped 1979;95:523–529.
396. Kaufman DV, Bostwick E. Defective suppressor T cell activity in systemic lupus erythematosus. Clin Immunol Immunopathol 1979;13:9–18.
397. Morimoto C, Abe T, Homma M. Altered function of suppressor T lymphocytes in patients with active systemic lupus erythematosus. Clin Immunol Immunopathol 1979; 13:161–170.
398. Newman B, Blank R, Lomnitzer R, Disler P, Rabson AR. Lack of suppressor activity in systemic lupus erythematosus. Clin Immunol Immunopathol 1979;13:187–193.
399. Bluestein HG, Zvaifler NJ, Weisman MH, Shapiro RE. Lymphocyte alteration by procainamide: relation to drug induced lupus erythematosus syndrome. Lancet 1979; ii:816–819.
400. Sagawa A, Abdou NI. Suppressor cell antibody in systemic lupus erythematosus. Possible mechanism for suppressor cell dysfunction. J Clin Invest 1979;63:536–539.
401. Ilfeld DN, Krakauer RS. Suppression of immunoglobulin synthesis of systemic lupus erythematosus patients by concanavalin A activated normal human spleen cell supernatants. Clin Immunol Immunopathol 1980;17:196–202.
402. Gladman D, Keystone E, Urowitz M, Cane D, Poplonski L. Impaired antigen specific suppressor cell activity in patients with systemic lupus erythematosus. Clin Exp Immunol 1980;40:77–82.
403. Alarcon-Segovia D, Palacios R. Differences in immunoregulatory T cell circuits between diphenylhydantoin related and spontaneously occurring SLE. Arthritis Rheum 1981; 24:1086–1092.
404. Coovadia HM, Mackay IR, d'Aspice AJF. Suppressor cells assayed by three different methods in patients with chronic active hepatitis and systemic lupus erythematosus. Clin Immunol Immunopathol 1981;18:268–275.
405. Miller KB, Schwartz RS. Autoimmunity and suppressor T lymphocytes. In Advances in Internal Medicine. G. Stollerman, ed. Chicago, Year Book Medical Publishers, Inc. 1982; 281–331.
406. Tsokos GC, Magrath IT, Balow JE. Epstein Barr virus induces normal B cell responses but defective T cell responses in patients with systemic lupus erythematosus. J Immunol 1983;131:1797–1801.
407. Schattner A, Miller KB, Kaburaki Y, Schwartz RS. Suppressor cell function and anti-DNA antibody idiotypes in the serum of SLE patients and their first-degree relatives. Clin Immunol Immunopathol 1986;41:417–426.
408. Warrington RJ, Rutherford WJ. Normal mitogen-induced suppression of the interleukin-6 (IL-6) response and its deficiency in systemic lupus erythematosus. J Clin Immunol 1990;10:52–60.
409. Tsokos, GC, Smith PL, Christian CB, Lipnick RN, Balow JE, Djeu JY. Interleukin-2 restores the depressed allogeneic cell-mediated lympholysis and natural killer cell activity in patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1985;34:379–386.
410. Via CS, Sharrow SO, Shearer GM. Role of cytotoxic T lymphocytes in the prevention of lupus-like disease occurring in a murine model of graft-vs-host disease. J Immunol 1987; 139:1840–1849.
411. Friedman SM, Posnett DN, Tumang JR, Cole BC, Crow MK. A potential role for microbial superantigens in the pathogenesis of systemic autoimmune disease. Arthritis Rheum 1991;34:468–480.
412. Takeda K, Dennert G. The development of autoimmunity in C57B1/6 *Ipr* mice correlates with the disappearance of natural killer type-1 positive cells: evidence for their suppressive action on bone marrow stem cell proliferation, 8 cell immunoglobulin secretion, and autoimmune symptoms. J Exp Med 1993;177:155–164.
413. Williams RC Jr, Lies RB, Messner RP. Inhibition of mixed leukocyte culture responses by serum and gamma globulin fractions from certain patients with connective tissue disorders. Arthritis Rheum 1973;16:597–605.
414. Hahn BH, Pletcher LS, Muniain M, MacDermott RP. Suppression of the normal autologous mixed lymphocyte reaction by sera from patients with systemic lupus erythematosus. Arthritis Rheum 1982;25:381–389.
415. Okudaira K, Searles RP, Goodwin JS, Williams RC Jr. Antibodies in the sera of patients with systemic lupus erythematosus that block the binding of monoclonal anti-Ia to Ia-positive targets also inhibit the autologous mixed lymphocyte response. J Immunol 1982;129:582–586.
416. Sakane T, Kotani H, Takada S, Murakawa Y, Ueda Y. A defect in the suppressor circuits among OKT4+ cell populations in patients with systemic lupus erythematosus occurs independently of a defect in the OKT8+ suppressor T cell function. J Immunol 1983;181:753–756.
417. Stephens HAF, Fitzharris P, Knight RA, Snaith ML. Inhibition of proliferative and suppressor responses in the autologous mixed lymphocyte reaction by serum from patients with systemic lupus erythematosus. Ann Rheum Dis 1982; 41:495–501.
418. Brozek CM, Hoffman CL, Savage SM, Searles RP. Systemic lupus erythematosus sera inhibit antigen presentation by macrophages to T cells. Clin Immunol Immunopathol 1988; 46:299–313.
419. Cohen PL, Litvin DA, Winfield JB. Association between endogenously activated T cells and immunoglobulin-secreting B cells in patients with active systemic lupus erythematosus. Arthritis Rheum 1982;25:168–173.
420. Litvin DA, Cohen PL, Winfield JB. Characterization of warm-reactive IgG anti-lymphocyte antibodies in systemic lupus erythematosus. Relative specificity for mitogen-activated T cells and their soluble products. J Immunol 1983; 130:181–186.

421. Sagawa A, Abdou NI. Suppressor-cell antibody in systemic lupus erythematosus. Possible mechanism for suppressor-cell dysfunction. J Clin Invest 1979;63:536–539.
422. Morimoto C, Abe T, Toguchi T, Kiyotaki H, Homma M. Studies of anti-lymphocyte antibody in patients with active SLE. Scand J Immunol 1979;10:213–221.
423. Sakane T, Steinberg AD, Reeves JP, Green I. Studies of immune functions of patients with systemic lupus erythematosus. 4. T-cell subsets and antibodies to T-cell subsets. J Clin Invest 1979;64:1260–1269.
424. Yamada A, Shaw M, Winfield JB. Surface antigen specificity of cold-reactive IgM antilymphocyte antibodies in systemic lupus erythematosus. Arthritis Rheum 1985;28:44–51.
425. Tanaka S, Matsuyama T, Steinberg AD, Schlossman SF, Morimoto C. Antilymphocyte antibodies against CD4+2H4+ cell populations in patients with systemic lupus erythematosus. Arthritis Rheum 1989;32:398–405.
426. Gorla R, Airo P, Franceschini F, Stefani E, Braga S, Tincani A, Cattaneo R. Decreased number of peripheral blood CD4+ CD29+ lymphocytes and increased spontaneous production of anti-DNA antibodies in patients with systemic lupus erythematosus. J Rheumatol 1990;17:1048–1053.
427. Messner RP, De Horatius RJ, Ferrone S. Lymphocytotoxic antibodies in systemic lupus erythematosus patients and their relatives. Reactivity with the HLA antigenic molecular complex. Arthritis Rheum 1980;23:265–272.
428. Drake CG, Rozzo SJ, Hirschfeld HF, Smarnworawong NP, Palmer E, Kotzin BL. Analysis of the New Zealand Black contribution to lupus-like renal disease. Multiple genes that operate in a threshold manner. J Immunol 1995:154:2441–2447.
429. Kono DH, Burlingame RW, Owens DG, Kuramochi A, Balderas RS, Balomenos D, Theofilopoulos AN. Lupus susceptibility loci in New Zealand mice. Proc Natl Acad Sci U S A 1994;91:10168–10172.
430. Drake CG, Rozzo SJ, Vyse TJ, Palmer E, Kotzin BL. In mice there is also evidence to suggest a role for MHC class I genes. Immunol Rev 1995;144:51–74.
431. Schur PH. Complement and lupus erythematosus. Arthritis Rheum 1982;25:793–798.
432. Crow MK, Zagon G, Chu Z, Ravina B, Tumang JR, Cole BC, Friedman SM. Human B cell differentiation induced by microbial superantigens: unselected peripheral blood lymphocytes secrete polyclonal immunoglobulin in response to Mycoplasma arthritidis mitogen. Autoimmunity 1992; 14:23–32.
433. Stohl W, Elliott JE. Differential human T cell-dependent B cell differentiation induced by staphylococcal superantigens (SAg): regulatory role for SAg-dependent B cell cytolysis. J Immunol 1995;155:1838–1850.
434. Cornacchia E, Golbus J, Maybaum J, Strahler J, Hanash S, Richardson B. Hydralazine and procainamide inhibit T cell DNA methylation and induce autoreactivity. J Immunol 1988;140:2197–2200.
435. Richardson BC, Liebling MR, Hudson JL. CD4+ cells treated with DNA methylation inhibitors induce autologous B cell differentiation. Clin Immunol Immunopathol 1990; 55:368–381.
436. Monestier M, Kotzin BL. Antibodies to histones in systemic lupus erythematosus and drug-induced lupus syndromes. Clin Rheum Dis 1992;18:415–436.
437. Amoura Z, Chabre H, Koutouzov S, Lotton C, Cabrespines A, Bach JF, Jacob L. Nucleosome restricted antibodies are detected before anti-dsDNA in the sera of MRL-Mp lpr/lpr and +/+ mice and are present in the kidney eluates of lupus mice with proteinuria. Arthritis Rheum 1994;37:1684–1688.
438. Gilkeson GS, Grudier JP, Karounos DG, Pisetsky DS. Induction of anti-double stranded DNA antibodies in normal mice by immunization with bacterial DNA. J Immunol 1989;142:1482–1486.
439. Jacob L, Lety MA, Louvard D, Bach JF. Binding of a monoclonal anti-DNA autoantibody to identical protein(s) present at the surface of several human cell types involved in lupus pathogenesis. J Clin Invest 1985;75:315–317.
440. Jacob L, Viard JP, Allenet B, Anin MF, Slama FBH, Vandekerckhove J, Primo J, Markovitz J, Jacob F, Bach JF, Le Pecq JB, Louvard D. A monoclonal anti-double-stranded DNA autoantibody binds to a 94-kDa cell-surface protein on various cell types via nucleosomes or a DNA-histone complex. Proc Natl Acad Sci U S A 1989;86:4669–4673.
441. Rieber M, Urbina C, Rieber MS. DNA on membrane receptors: a target for monoclonal anti-DNA antibody induced by a nucleoprotein shed in systemic lupus erythematosus. Biochem Biophys Res Commun 1989;159:1441–1447.
442. Pham BN, Prin L, Gosset D, Hatron PY, Devulder B, Capron A, Dessaint JP. T lymphocyte activation in systemic lupus erythematosus analyzed by proliferative response to nucleoplasmic proteins on nitrocellulose immunoblots. Clin Exp Immunol 1989;77:168–174.
443. Burlingame RW, Rubin RL, Balderas RS, Theophilopoulos AN. Genesis and evolution of anti-chromatin autoantibodies in murine lupus implicates T-dependent immunization with self-antigen. J Clin Invest 1993;91:1687–1696.
444. Burlingame RW, Boey ML, Starkebaum G, Rubin RL. The central role of chromatin in autoimmune responses to histones and DNA in systemic lupus erythematosus. J Clin Invest 1994;94:184–192.
445. Mohan C, Datta SK. Lupus: key pathogenic mechanisms and contributing factors. Clin Immunol Immunopathol 1995;77:209–220.
446. Gleichmann E, Pals ST, Rolink AG, Radaskiewicz T, Gleichmann H. Graft-versus-host reactions: clues to the etiopathology of a spectrum of immunological diseases. Immunol Today 1984;5:324–332.
447. Gleichmann E, Van Elven EH, Van der Veen JP. A systemic lupus erythematosus (SLE)-like disease in mice induced by abnormal T-B cell cooperation. Preferential formation of autoantibodies characteristic of SLE. Eur J Immunol 1982; 12:152–159.
448. Carson DA, Chen PP, Kipps TJ. New roles for rheumatoid factor. J Clin Invest 1991;87:379–383.
449. Rolink AG, Gleichmann E. Allosuppressor- and allohelper-T cells in acute and chronic graft-vs.-host (GVH) disease. III. Different Lyt subsets of donor T cells induce different pathological syndromes. J Exp Med 1983;158:546–558.
450. Pals ST, Gleichmann H, Gleichmann E. Allosupressor and allohelper T cells in acute and chronic graft-vs.-host disease. V. F_1 mice with secondary chronic GVHD contain F1-reactive allohelper but no allosuppressor T cells. J Exp Med 1984;159:508–523.
451. Takeda K, Dennert G. The development of autoimmunity in C57BL/6 lpr mice correlates with the disappearance of natural killer type 1–positive cells: evidence for their suppressive action on bone marrow stem cell proliferation, B cell immunoglobulin secretion, and autoimmune symptoms. J Exp Med 1993;177:155–164.
452. Raptis L, Menard HA. Quantitation and characterization of plasma DNA in normals and patients with systemic lupus erythematosus. J Clin Invest 1980;66:1391–1399.
453. McCourbrey-Hoyer A, Okarma TB, Holman HR. Partial characterization of plasma DNA and its relation to disease

activity in systemic lupus erythematosus. Am J Med 1984; 77:23–24.
454. Steinman CR. Circulating DNA in systemic lupus erythematosus. J Clin Invest 1984;73:832–841.
455. Owen-Schaub LB, Yonehara S, Crump WL III, Grimm EA. DNA fragmentation and cell death is selectively triggered in activated human lymphocytes by Fas antigen engagement. Cell Immunol 1992;140:197–205.
456. Nishioka WK, Welsh RM. Susceptibility to cytotoxic T lymphocyte-induced apoptosis is a function of the proliferative status of the target. J Exp Med 1994;179:769–774.
457. Emlen W, Niebur J, Kadera R. Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. J Immunol 1994;152:3685–3692.
458. Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH. Defective reticuloendothelial system Fc-receptor function in systemic lupus erythematosus. N Engl J Med 1979; 300:518–523.
459. Robey FA, Jones KD, Steinberg AD. C-reactive protein mediates the solubilization of nuclear DNA by complement in vitro. J Exp Med 1985;161:1344–1356.
460. Bennet RM, Kotzin BL, Merritt MJ. DNA receptor dysfunction in systemic lupus erythematosus and kindred disorders. J Exp Med 1987;166:850–863.
461. Du Clos TW, Zlock LT, Hicks PS, Mold C. Decreased autoantibody levels and enhanced survival of (NZBxNZW) F1 mice teated with C-reactive protein. Clin Immunol Immunopathol 1994;70:22–27.
462. Horwitz DA, Linker-Israeli M, Gray JD, Lemoine C. Functional properties of CD8 positive lymphocyte subsets in systemic lupus erythematosus. J Rheumatol 1987;14:49–52.
463. Mohan C, Shi Y, Laman JD, Datta SK. Interaction between CD40 and its ligand GP39 in the development of murine lupus nephritis. J Immunol 1995;154:1470–1480.
464. Horwitz DA. Selective depletion of B lymphocytes with cyclophosphamide in patients with rheumatoid arthritis and systemic lupus erythematosus: guidelines for dosage. Arthritis Rheum 1974;17:363–374.
465. Dau PC, Callahan J, Parker R, Golbus J. Immunologic effects of plasmapheresis synchronized with pulse cyclophosphamide in systemic lupus erythematosus (case report). J Rheumatol 1991;18:270–276.
466. Jondal M, Pross H. Surface markers on human B and T lymphocytes. VI. Cytotoxicity against cell lines as a functional marker for lymphocyte subpopulations. Int J Cancer 1975;15:596–605.
467. Takasugi M, Mickey MR, Terasaki PI. Reactivity of lymphocytes from normal persons on cultured tumor cells. Cancer Res 1973;33:2898–2902.
468. West WH, Cannon GD, Kay HD, Blonnard GD, Herberman RB. Natural cytotoxic reactivity of human lymphocytes against a myeloid cell line: characterization of the effector cells. J Immunol 1977;118:355–361.
469. Biron CA, Byron KS, Sullivan JL. Susceptibility to viral infections in an individual with a complete lack of natural killer cells. Nat Immun Cell Growth Regul 1988;7:47–49.
470. Abo W, Gray JD, Baake AC, Horwitz DA. Studies on human blood lymphocytes with iC3b (type 3) complement receptors. II. Characterization of subsets which regulate pokeweed mitogen-induced lymphocyte proliferation and immunoglobulin synthesis. Clin Exp Immunol 1987; 67:554–564.
471. Kuwano KK, Arai S, Munakata T, Tomita Y, Yoshitake Y, Kumagai K. Suppressive effect of human natural killer cells on Epstein-Barr virus-induced immunoglobulin synthesis. J Immunol 1986;137:1462–1468.
472. Vyakarnam A, Brenner MK, Reittie JE, Houlker CH, Lachmann PJ. Human clones with natural killer function can activate B cells and secrete B cell differentiation factors. Eur J Immunol 1985;15:606–610.
473. Griffin JD, Hercend T, Beveridge R, Schlossman SF. Characterization of an antigen expressed by human natural killer cells. J Immunol 1983;130:2947–2951.
474. Zarling JM, Clouse JA, Biddison WE, Kung PC. Phenotypes of human natural killer cells populations detected with monoclonal antibodies. J Immunol 1981;127:2575–2580.
475. Lanier LL, Benike CJ, Phillips JH, Engleman EG. Recombinant interleukin 2 enhanced natural killer cell-mediated cytotoxicity in human lymphocyte populations expressing Leu 7 and Leu 11 antigens. J Immunol 1985;134:794–801.
476. Hercend T, Griffin Bensussan A, Schmidt RE, Edson MA, Brennan A, Murray C, Daley JF, Schlossman SF, Ritz J. Generation of monoconal antibodies to a human natural killer clone. Characterization of two natural killer-associated antigens, NKH1A and NKH2, expressed on a subset of large granular lymphocytes. J Clin Invest 1985;75:932–943.
477. Kay HD, Horwitz DA. Evidence by reactivity with hybridoma antibodies for a probable myeloid origin of peripheral blood cells active in natural cytotoxicity and antibody-dependent cell-mediated cytotoxicity. J Clin Invest 1980; 66:847–851.
478. Lanier LL, Cwirla S, Yu G, Testi R, Phillips JH. Membrane anchoring of a human IgG Fc receptor (CD16) determined by a single amino acid. Science 1989;246:1611–1613.
479. Perussia B, Starr S, Abraham S, Fanning V, Trinchieri G. Human natural killer cells analyzed by B73.1, a monoclonal antibody blocking Fc receptor functions. I. Characterization of the lymphocyte subset reactive with B73.1. J Immunol 1983;130:2133–2141.
480. Ross GD, Medof ME. Membrane complement receptors specific for bound fragments of C3. Adv Immunol 1985; 37:217–267.
481. Dustin ML, Springer TA. Role of lymphocyte adhesion receptors in transient interactions and cell locomotion. Annu Rev Immunol 1991;9:27–66.
482. Patarroyo M. Leucocyte adhesion to cells. Molecular basis, physiological relevance, and abnormalities. Scand J Immunol 1989;30:129–164.
483. Ravetch JV, Kinet JP. Fc receptors. Annu Rev Immunol 1991;9:457–492.
484. Lanier LL, Phillips JM, Hackett J, Tutt M, Kumar V. Natural killer cells: definition of a cell type rather than a function. J Immunol 1986;137:2735–2739.
485. Bakke AC, Gray JD, Abo W, Quismorio FP, Lash A, Cooper SM, Horwitz DA. Studies on human blood lymphocytes with iC3b (type 3) complement receptors. I. Granular, Fc-IgG receptor positive and negative subsets in healthy subjects and patients with systemic lupus erythematosus. J Immunol 1986;136:1253–1259.
486. Werfer T, Witter W, Gotze O. CD11b and CD11c antigens are rapidly increased in human natural killer cells upon activation. J Immunol 1991;147:2423–2427.
487. Gray JD, Horwitz DA. Lymphocytes expressing type 3 complement receptors proliferate in response to interleukin 2 and are the precursors of lymphokine-activated killer cells. J Clin Invest 1988;81:1247–1254.
488. Lanier LL, Le AM, Civin CI, Loken MR, Phillips JH. The relationship of CD16 (Leu-11) and Leu-19 (NKH-1) antigen expression on human peripheral blood NK cells and cytotoxic T lymphocytes. J Immunol 1986;136:4480–4486.
489. Domzig W, Stadler BM, Herberman RB. Interleukin 2 dependence on human natural killer cell activity. J Immunol 1983;130:1970–1973.

490. Trinchieri G, Santoli D. Antiviral activity induced by culturing lymphocytes with tumor-derived or virus-transferred cells. Enhancement of human natural killer cell activity by interferon and inhibition of susceptibility of target cells to lysis. J Exp Med 1978;147:1314–1333.
491. Alarcon-Segovia D, Ruiz-Arguelles A. Decreased circulating thymus-derived cells with receptors for the Fc portion of immunoglobulin G in systemic lupus erythematosus. J Clin Invest 1978;62:1390–1394.
492. Fauci AS, Steinberg AD, Haynes BF, Whalen G. Immunoregulatory aberrations in systemic lupus erythematosus. J Immunol 1978;121:1473–1479.
493. Gray JD, Lash A, Baake AC, Horwitz DA. Studies on human blood lymphocytes with iC3b (type 3) complement receptors: III. Abnormalities in patients with active systemic lupus erythematosus. Clin Exp Immunol 1987;67:556–564.
494. Struyf NJ, Snoeck HW, Bridts CH, DeClerck LS, Stevens WJ. Natural killer cell activity in Sjogren's syndrome and systemic lupus erythematosus: stimulation with interferons and interleukin 2 and correlation with immune complexes. Ann Rheum Dis 1990;49:690–693.
495. Goto M, Tanimoto K, Horiuchi Y. Natural cell mediated cytotoxicity in systemic lupus erythematosus. Suppression by anti-lymphocyte antibody. Arthritis Rheum 1980; 23:1274–1281.
496. Hoffman T. Natural killer function in systemic lupus erythematosus. Arthritis Rheum 1980;23:30–35.
497. Katz P, Zaytoun AM, Lee JH Jr, Panush RS, Longley S. Abnormal natural killer cell activity in systemic lupus erythematosus: an intrinsic defect in the lytic event. J Immunol 1982;129:1966–1971.
498. Oshimi K, Sumiya M, Gonda N, Kano S, Takaku F. Natural killer cell activity in untreated systemic lupus erythematosus. Ann Rheum Dis 1982;41:417–420.
499. Rook AH, Tsokos GC, Quinnan GV Jr, Balow JE, Ramsey KM, Stocks N, Phelan MA, Djeu JY. Cytotoxic antibodies to natural killer cells in systemic lupus erythematosus. Clin Immunol Immunopathol 1982;24:179–185.
500. Silverman SL, Cathcart ES. Natural killing in systemic lupus erythematosus: inhibitory effects of serum. Clin Immunol Immunopathol 1980;17:219–226.
501. Perussia B, Acuto O, Terhorst C, Faust J, Lazarus R, Fanning V, Trinchieri G. Human natural killer cells analyzed by B73.1, a monoclonal antibody blocking FcR functions. II. Studies of B73.1 antibody-antigen interaction on the lymphocyte membrane. J Immunol 1983;130:2142–2148.
502. Schur PH. Complement and immune complexes in systemic lupus erythematosus. In: Wallace DJ, Dubois EL, eds. Dubois' lupus erythematosus. 3rd ed. Philadelphia: Lea & Febiger, 1987;185–193.
503. Sipos A, Csortos C, Sipka S, Gergely P, Sonkoly I, Szegedi G. The antigen/receptor specificity of antigranulocyte antibodies in patient with SLE. Immunol Lett 1988;19:329–334.
504. Diaz-Jouanen E, Bankhurst AD, Williams RC. Antibody-mediated lymphocytotoxicity in rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum 1976; 19:133–141.
505. Feldmann J, Becker MJ, Moutsopoulos H, Fye K, Blackman M, Epstein WV, Talal N. Antibody dependent cell-mediated cytotoxicity in selected autoimmune diseases. J Clin Invest 1976;58:173–179.
506. Scheinberg MA, Cathcart ES. Antibody-dependent direct cytotoxicity of human lymphocytes. I. Studies on peripheral blood lymphocytes and sera of patients with systemic lupus erythematosus. Clin Exp Immunol 1976;24:317–322.
507. Schneider J, Chin W, Friou GJ, Cooper SM, Harding B, Hill RL, Quismorio FP. Reduced antibody-dependent cell-mediated cytotoxicity in systemic lupus erythematosus. Clin Exp Immunol 1975;20:187–192.
508. Kumagai S, Steinberg AD, Green I. Antibodies to T cells in patients with systemic lupus erythematosus can induce antibody-dependent cell-mediated cytotoxicity against human T cells. J Clin Invest 1981;67:605–614.
509. Brunda MJ, Tarnowski D, Davatelis V. Interaction of recombinant interferons with recombinant interleukin-2: differential effects on natural killer cell activity and interleukin-2-activated killer cells. Int J Cancer 1986;37:787–793.
510. Phillips JH, Lanier LL. Dissection of the lymphokine-activated killer phenomenon. Relative contribution of peripheral blood natural killer cells and T lymphocytes to cytolysis. J Exp Med 1986;164:814–825.
511. Svedersky LP, Shepard HM, Spencer SA, Shalaby MR. Augmentation of human natural cell-mediated cytotoxicity by recombinant human interleukin 2. J Immunol 1984; 133:714–718.
512. Trinchieri G, Matsumoto-Kobayashi M, Clark SC, Sjeehra J, London L, Perussia B. Response of resting human peripheral blood natural killer cells to interleukin-2. J Exp Med 1984;160:1147–1169.
513. Sibbitt WL Jr, Likar L, Spellman CW, Bankhurst AD. Impaired natural killer cell function in systemic lupus erythematosus. Relationship to interleukin-2 production. Arthritis Rheum 1983;26:1316–1320.
514. Ling MHM, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy. Arch Gen Psychiatry 1981;38:471–477.
515. Grimm EA, Mazumder A, Zhang HZ, Rosenberg SA. Lymphokine-activated killer cells phenomenon. Lysis of natural killer-resistant fresh solid tumor cells by interleukin 2-activated autologous human peripheral blood lymphocytes. J Exp Med 1982;155:1823–1841.
516. Phillips JH, Gemlo BT, Myers WW, Rayner AA, Lanier LL. In vivo and in vitro activation of natural killer cells in advanced cancer patients undergoing combined recombinant interleukin-2 and LAK cell therapy. J Clin Oncol 1987; 5:1933–1941.
517. Rosenberg S. Lymphokine-activated killer cells: a new approach to A immunotherapy of cancer. J Natl Cancer Inst 1985:75:595–603.
518. Froelich CJ, Guiffaut S, Sosenko M, Muth K. Deficient interleukin-2-activated killer cell cytotoxicity in patients with systemic lupus erythematosus. Clin Immunol Immunopathol 1989;50:132–145.
519. Arai S, Yamamoto H, Itoh K, Kumagai K. Suppressive effect of human natural killer cells on pokeweed mitogen-induced B cell differentiation. J Immunol 1983;131:651–657.
520. Brieva JA, Targan S, Stevens RH. NK and T cell subsets regulate antibody production by human in vivo antigen-induced lymphoblastoid B cells. J Immunol 1983;132:611–615.
521. Tilden AV, Abo T, Balch CM. Suppressor cell function of human granular lymphocytes identified by the HNK-1 (Leu 7) monoclonal antibody. J Immunol 1983;130:1171–1175.
522. Katz P, Mitchell SR, Cupps TR, Evans M, Whalen G. Suppression of B cell responses by natural killer cells is mediated through direct effects on T cells. Cell Immunol 1989; 119:130–142.
523. Yuan D, Koh CY, Wilder JA. Interactions between B lymphocytes and NK cells. FASEB J 1994;8:1012–1018.
524. Huston DP, Che S. Natural killer cell suppression of IgM production. Nat Immun 1994;13:258–269.
525. Gray JD, Hirokawa M, Horwitz DA. The role of transforming growth factor β in the generation of suppression: an

interaction between CD8+ T and NK cells. J Exp Med 1994;180:1937–1942.
526. Sporn MB, Roberts AB, Wakefield LM, De Crombrugghe B. Some recent advances in the chemistry and biology of TGFβ. J Cell Biol 1987;105:1039–1045.
527. Wahl SM. Transforming growth factor β: the good, the bad, and the ugly. J Exp Med 1994;180:1587–1590.
528. Harada M, Lin T, Kurosawa S, Maeda T, Umesue M, Itoh O, Matsuzaki G, Nomoto K. Natural killer cells inhibit the development of autoantibody production in (C57BL/6 x DBA/2)F1 hybrid mice injected with DBA/2 spleen cells. Cell Immunol 1995;161:42–49.
529. Pan LZ, Dauphinee MJ, Ansar Ahmed S, Talal N. Altered natural killer and natural cytotoxic cellular activities in lpr mice. Scand J Immunol 1986:23:415–423.
530. Kimata H, Shanahan F, Brogan M, Targan S, Saxon A. Modulation of ongoing human immunoglobulin synthesis by natural killer cells. Cell Immunol 1987;107:74–88.
531. Brenner MK, Vyakarnam A, Reittie JE, Wimperis JZ, Grob JP, Hoffbrand AV, Prentice HG. Human large granular lymphocytes induce immunoglobulin synthesis after bone marrow transplantation. Eur J Immunol 1987;17:43–47.
532. Procopio ADG, Allavena P, Ortaldo JR. Noncytotoxic functions of natural killer (NK) cells: large granular lymphocytes (LGL) produce a B cell growth factor (BCGF). J Immunol 1985;135:3264–3271.
533. Becker JC, Kolanus W, Lonnemann C, Schmidt RE. Human natural killer clones enhance in vitro antibody production by tumor necrosis factor alpha and gamma interferon. Scand J Immunol 1990;32:153–162.
534. Jelinek DF, Lipsky PE. Enhancement of human B cell proliferation and differentiation by tumor necrosis factor-α and interleukin 1. J Immunol 1987;139:2970–2976.
535. Kimata H, Sherr EH, Saxon A. Human natural killer (NK) cells produce a late-acting B-cell differentiation activity. J Clin Immunol 1988;8:381–389.
536. Parker DC. T cell-dependent B cell activation. Annu Rev Immunol 1993;11:331–360.

Dubois' Lupus Erythematosus

Fifth Edition

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Accurate indications, adverse reactions and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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1 2 3 4 5 6 7 8 9 10

Contents

Dedication v

Preface vii

Contributors ix

Section I. The History of Lupus Erythematosus

1. Historical Background of Discoid and Systemic Lupus Erythematosus 3
Thomas G. Benedek

Section II. Definition, Classification and Epidemiology of Lupus

2. Definition, Classification, Activity, and Damage Indices 19
Kenneth C. Kalunian

3. The Role of the Environment in Systemic Lupus Erythematosus and Associated Disorders 31
Anne-Barbara Mongey and Evelyn V. Hess

4. The Epidemiology of Systemic Lupus Erythematosus 49
Marc C. Hochberg

Section III. The Pathogenesis of Lupus Erythematosus

5. An Overview of the Pathogenesis of Systemic Lupus Erythematosus 69
Bevra H. Hahn

6. The Genetics of Human Lupus 77
Frank C. Arnett, Jr.

7. The Genetics of Murine Systemic Lupus Erythematosus 119
Dwight H. Kono and Argyrios N. Theofilopoulos

8. Apoptosis 133
Keith B. Elkon

9. Tolerance Abnormalities in Systemic Lupus Erythematosus
Betty P. Tsao 143

10. The Role of T Lymphocytes in SLE
David Horowitz 155

11. B-Cell Abnormalities Characteristic of Systemic Lupus Erythematosus
Dennis M. Klinman 195

12. Immune Complexes in Systemic Lupus Erythematosus
V. Joyce Gauthier and J. Woodruff Emlen 207

13. Abnormalities in Immune Complex Clearance and FCγ-Receptor Function
Jane E. Salmon 221

14. Complement and Systemic Lupus Erythematosus
Peter H. Schur 245

15. Mechanisms of Acute Inflammation and Vascular Injury in Systemic Lupus Erythematosus
H. Michael Belmont and Steven Abramson 263

16. Eicosanoids in SLE
Dwight R. Robinson 279

17. Idiotypes and Idiotype Networks
Bevra H. Hahn and Fanny M. Ebling 291

18. The Importance of Sex Hormones in Lupus
Sara E. Walker 311

19. Neuroendocrinology, Stress and Lupus
Esther M. Sternberg 323

20. Animal Models of Systemic Lupus Erythematosus
Bevra H. Hahn 339

Section IV. Autoantibodies

21. The Structure and Derivation of Antibodies and Autoantibodies
Chaim Putterman, Philip Kuo, and Betty Diamond 383

22. Antinuclear Antibodies: An Overview
Morris Reichlin and John B. Harley 397

23. Antibodies to DNA
Bevra H. Hahn and Betty P. Tsao 407

24. Antibodies to Histone and the Role of the Nucleosome
Marvin J. Fritzler 423

25. Antibodies to Ro/SSA and La/SSB
John B. Harley and Morris Reichlin 443

26. Anti-snRNP Antibodies
Joseph E. Craft 457

27. Antiphospholipid Antibodies
Azzudin E. Gharavi and Wendell A. Wilson 471

28. The Lupus Anticoagulant and Antiphospholipid Antibodies
Gail A. McCarty 493

29. Antilymphocyte Autoantibodies
John B. Winfield 505

30. Antibodies to Brain
Harry G. Bluestein 517

31. Other Serologic Abnormalities in Systemic Lupus Erythematosus
Francisco P. Quismorio, Jr. 523

Section V. Cutaneous Lupus

32. Overview of Cutaneous Lupus
Daniel J. Wallace 547

33. Pathomechanisms of Cutaneous Lupus Erythematosus
David A. Norris, Col. Scott D. Bennion, and Lt. Col. Kathleen M. David-Bajar 549

34. Cutaneous Manifestations of Lupus Erythematosus
Richard D. Sontheimer and Thomas T. Provost 567

Section VI. Clinical and Laboratory Features of Systemic Lupus Erythematosus

35. The Clinical Presentation of Systemic Lupus Erythematosus
Daniel J. Wallace 627

36. The Musculoskeletal System
Daniel J. Wallace 635

37. Cardiac Abnormalities in Systemic Lupus Erythematosus
Francisco P. Quismorio, Jr. 653

38. Pulmonary Manifestations of Systemic Lupus Erythematosus
Francisco P. Quismorio, Jr. 673

39. Cutaneous and Cutaneovascular Manifestations of Systemic Lupus Erythematosus
Daniel J. Wallace 693

40. Systemic Lupus Erythematosus and the Nervous System
Daniel J. Wallace and Allan L. Metzger 723

41. Psychopathology in the Patient with Lupus
Howard S. Shapiro 755

42. Head and Neck Findings in Systemic Lupus Erythematosus: Sjögren's Syndrome and the Eye, Ear, and Larynx
Juan-Manuel Anaya and Norman Talal 783

43. Hematologic and Lymphoid Abnormalities in Systemic Lupus Erythematosus
Francisco P. Quismorio, Jr. 793

44. The Endocrine System, Use of Exogenous Estrogens, and the Urogenital Tract
Jill P. Buyon and Daniel J. Wallace 817

45. Gastrointestinal and Hepatic Manifestations
Daniel J. Wallace 835

46. Systemic Lupus Erythematosus in Childhood and Adolescence
Thomas J.A. Lehman 851

47. Drug-Induced Lupus
Robert L. Rubin 871

48. Infections in Systemic Lupus Erythematosus
Ellen M. Ginzler 903

49. Serum and Plasma Protein Abnormalities and Other Clinical Laboratory Determinations in Systemic Lupus Erythematosus
Daniel J. Wallace 915

50. Clinical Application of Serologic Abnormalities in Systemic Lupus Erythematosus 925
Francisco P. Quismorio, Jr.

51. Differential Diagnosis and Disease Associations 943
Daniel J. Wallace

52. The Mother in Systemic Lupus Erythematosus 967
Rodanthi C. Kitridou

53. The Fetus in Systemic Lupus Erythematosus 1003
Rodanthi C. Kitridou

54. Neonatal Lupus Erythematosus 1023
Rodanthi Kitridou

55. Lupus Nephritis: Pathology, Pathogenesis, Clinical Correlations, and Prognosis 1037
Michael Kashgarian

56. Lupus Nephritis 1053
Daniel J. Wallace, Bevra H. Hahn, and John H. Klippel

57. Clinical and Management Aspects of the Antiphospholipid Syndrome 1067
Michelle Petri

Section VII. Management and Prognosis

58. Principles of Therapy and Local Measures 1099
Daniel J. Wallace

59. Salicylate and Nonsteroidal Therapy 1109
Philip J. Clements and Harold E. Paulus

60. Antimalarial Therapies 1117
Daniel J. Wallace

61. Systemic Corticosteroid Therapy in Systemic Lupus Erythematosus 1141
Francisco P. Quismorio, Jr.

62. Cytotoxic Drugs 1163
W. Joseph McCune

63. Nonpharmacologic Therapeutic Modalities 1181
Daniel J. Wallace

64. Occasional, Innovative, and Experimental Therapies 1191
Daniel J. Wallace

65. Adjunctive Measures and Issues: Allergies, Antibiotics, Vaccines, Hormones, and Osteoporosis 1203
Daniel J. Wallace and Bevra H. Hahn

66. Prognostic Subsets and Mortality in Systemic Lupus Erythematosus 1213
Dafna D. Gladman and Murray B. Urowitz

Afterword: The Future of Systemic Lupus Erythematosus: A Look Ahead 1229
Bevra H. Hahn

Section VIII. Appendices

Appendix 1: A Patient's Guide to Lupus Erythematosus 1237
Daniel J. Wallace, Bevra H. Hahn, and Francisco P. Quismorio, Jr.

Appendix 2: Lupus Resources for Patients, Physicians, and Health Professionals 1251
John M. Huber and Janice Beth Stoughton